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Supporting information

Cisplatin-assisted formation of organic nanotubes by endo-complexation in the cylindrical nanospace

Wuxiao Ding,[a] Momoyo Wada,[a] Hiroyuki Minamikawa,[a] Naohiro Kameta,[a] Mitsutoshi Masuda,*[a] and Toshimi Shimizu[a]

Nanotube Research Center

National Institute of Advanced Industrial Science and Technology (AIST)

Tsukuba Central 5, Higashi 1-1-1, Tsukuba 305-8565, Ibaraki, Japan

Tel.: 81-29-861-4615; Fax: 81-29-861-4545.

E-mail address: m-masuda@aist.go.jp

1. Synthesis of glycolipid

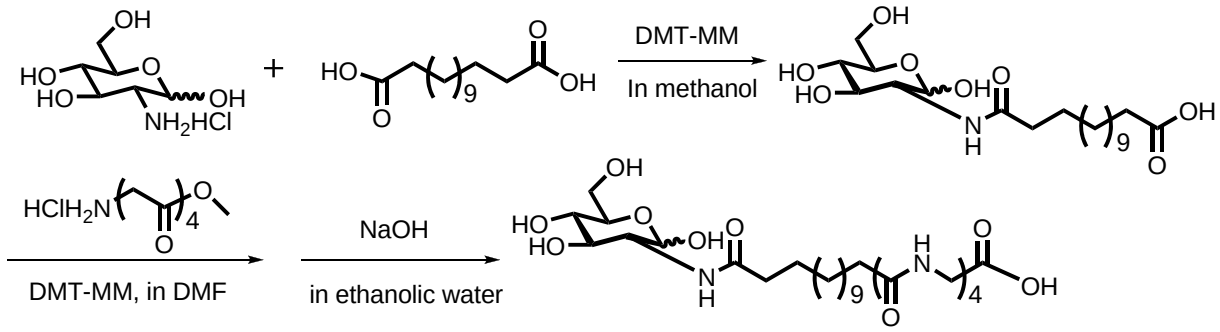

Figure S1 Synthesis of glycolipid **1**

1,12-Dodecanedicarboxylic acid (2.4 g, 9.3 mmol) was dissolved in methanol (100 mL), and 2-glucosamine hydrochloride (3 g, 13.9 mmol) was dispersed in water-methanol mixture (10 mL, 1/1 of v/v) containing NaOH (560 mg, 14 mmol). 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methyl morpholinium chloride (DMT-MM, 2.6 g, 9.3 mmol) and the 2-glucosamine solution were sequentially added into the 1,12-dodecanedicarboxylic acid solution. The mixture became opaque within 30 minutes and was stirred overnight at room temperature. The white suspension was filtered and washed by methanol to get intermideate **2** without further purification (2.73 g, 70% in yield).

To a solution of **2** (200 mg, 476 μmol) in dimethylformamide (DMF, 10 mL), glycyl-glycyl-glycyl-glycine methylester (136 mg, 525 μmol) and DMT-MM (186 mg, 570 μmol) were added and stirred for 4 h at room temperature. The reaction mixture was evaporated, re-dispersed by methanol, and filtered. The filtrate was re-suspended in ethanol-water solution (40 mL) containing NaOH (700 μmol) for hydrolysis at 60 ºC until the suspension turned clear. Hydrochloric acid (1N) was added to the solution to adjust pH 4, and white solid precipitated in the meantime. Filtration by polycarbonate membrane (pore size 200 nm) afforded **1** as a white powder (243 mg, 78%). ^{1}H-NMR (400 MHz, DMSO-d_6/D_2O, 60 ºC, δ): 7.61 and 8.14 (m, 5H; -CON***H***-), 4.91(d, J=3.3Hz, 0.7H; H-1α of glucosamine), 4.42(d, J=8.0Hz, 0.3H; H-1β of glucosamine), 3.75 and 3.83 (d, 8H; -NHC***H*****$_2$**CO-), 2.07-2.15(m, 4H; -NHCOC***H*****$_2$**-), 1.47(m, 4H; -NHCOCH$_2$C***H*****$_2$**-), 1.23(s, 16H; -C***H*****$_2$**-).

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Anal. Calcd for $C_{28}H_{49}N_5O_{12}\cdot 2H_2O$: C, 49.18; H, 7.81; N, 10.24; O, 32.77. Found; C, 49.09; H, 7.63; N, 10.37; O, 32.91.

*2. Time-dependent association of CDDP with **1**-Na and **1***

The bare ONT of **1** was prepared from the pH adjustment of **1**-Na solution to pH 4. The sodium chloride can be removed by membrane filtration (100-nm pore size) since the ONT essentially could not pass through the membrane pores as the length is over several micrometers.

A solution of **1**-Na or **1** (4.3 mg/mL in Milli-Q, 5 mL) was mixed with CDDP solution (1 mg/mL in Milli-Q, 10 mL) at the initial CDDP/**1**-Na or CDDP/**1** molar ratio of 1/1. The mixture was incubated at room temperature for 2, 8, 24, 48, 72, and 96 h. At each time point, 1 mL of the reaction mixture was sampled and subjected to a chamber filled with acetic acid vapor for 10 min to ensure that all the excess **1**-Na transform into the acidic form **1**. The mixture was then filtrated through a membrane filter (100-nm pore size) for the measurement of unreacted CDDP, and its concentration was determined with o-phenylenediamine colorimetric method at 703 nm.[1,2] The amount of reacted CDDP was calculated according to a calibration curve (in water, Figure S2) and expressed as associated CDDP/**1**-Na or CDDP/**1** (molar ratios) as shown in Figure 3 in main text.

The FT-IR spectra of mixture solution of CDDP and **1**-Na at 0 h and 48 h incubation were recorded by FT-620 (JASCO, Tokyo, Japan). For STEM observation, mixture solution at 2, 8, 24, and 48 h incubation were dropped onto a carbon grid, dried, and negatively stained with phosphotungstate solution (2 wt%, pH 5.0) for STEM observation with a Hitachi S-4800 microscope (Tokyo, Japan). The XRD patterns of bare ONT (**1**), CDDP@ONT, and nanofibers (**1**-Na) prepared by lyophilization of their solutions were measured with a Rigaku diffractometer (Type 4037) using graded *d*-space elliptical side-by-side multilayer optics, monochromated Cu-Kα radiation (40 kV, 30 mA), and an imaging plate (R-Axis IV). The exposure time was 30 min with a 150 nm camera length.

3. Release of CDDP@ONT in HEPES and HBS buffer

The brittle gel (Figure S6) containing CDDP@ONT and excess CDDP was physically agitated into a sol and filtrated though a membrane filter (100-nm pore size) to get CDDP@ONT, which was redispersed in Milli-Q as a fine solution (concentration of **1** about 2.3 mg/mL, and CDDP about 0.47 mg/mL). 1 mL of the CDDP@ONT solution was dispersed in HEPES buffer (9 mL, pH 7.4) or in HBS buffer (9 mL, HEPES-buffer saline, chloride 150 mM, pH 7.4) for release experiment over 96 h. At each time point, 1 mL of the release solution was sampled and subjected to acetic acid chamber for 10 min to ensure that dissociated **1**-Na transform into the acidic form **1**. The solutions were filtrated to isolated liberated CDDP as mentioned above. Its concentration was similarly determined according to a calibration curves (Figure S2) and expressed as CDDP released (%) as shown in Figure 4. The solutions after release experiment (96) were dropped onto a carbon grid, dried, and negatively stained with phosphotungstate solution (2 wt%, pH 5.0) for STEM observation.

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Reference:

1. M. Yokoyama, T. Okano, Y. Sakurai, S. Suwa and K. Kataoka, *J. Control. Release* 1996, **39**, 351.
2. J. K. Kim, J. Anderson, H. W. Jun, M. A. Repka and S. Jo, *Mol. Pharm*. 2009, **6**, 978.

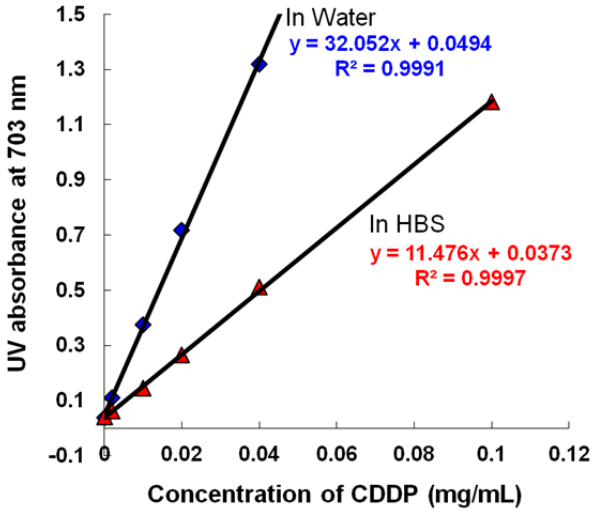

Figure S2 Calibration curves of CDDP in water and HBS buffer. The calibration curves were linear with correlation coefficients higher than 0.999 over the concentration range of 2–100 μg/mL. The relative lower detection sensitivity in HBS buffer might attribute to the ions in HBS buffer.

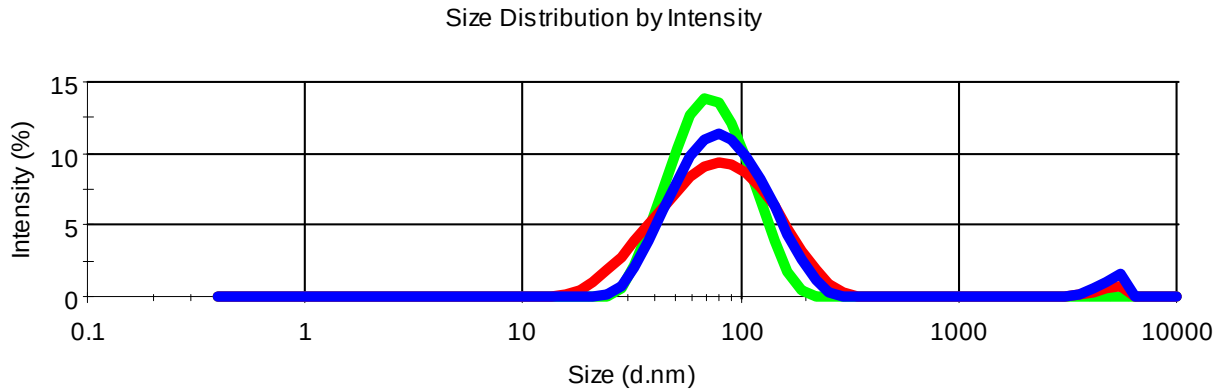

Figure S3 Dynamic light scattering of **1**-Na dispersion in water (2 mg/mL). Green line, at room temperature; Blue line, at 4 ºC; and Red line, at 50 ºC.

The **1**-Na dispersion has a mean hydrodynamic size of 50–70 nm, and the size was temperature-independent. This size was larger than that of common spherical micelles (up to around 10 nm).

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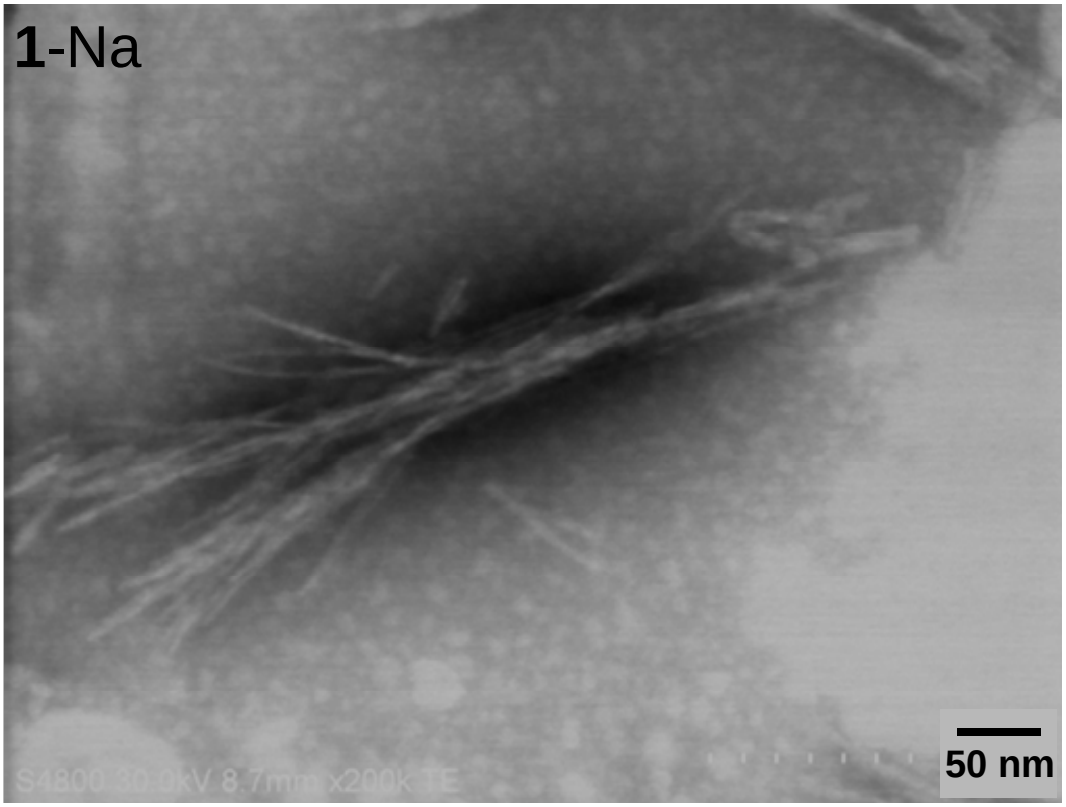

Figure S4 Nanofibers obtained from **1**-Na. The sample solution was rapidly evaporated on a carbon grid and stained with 2%-phosphotungstate (pH 8).

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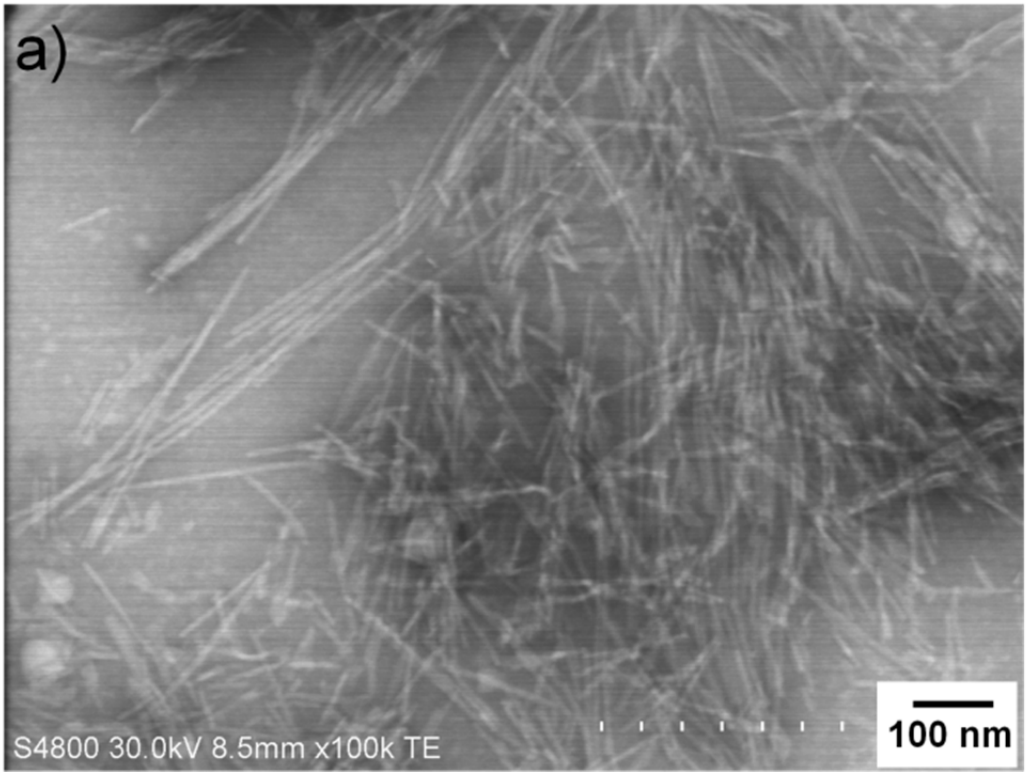

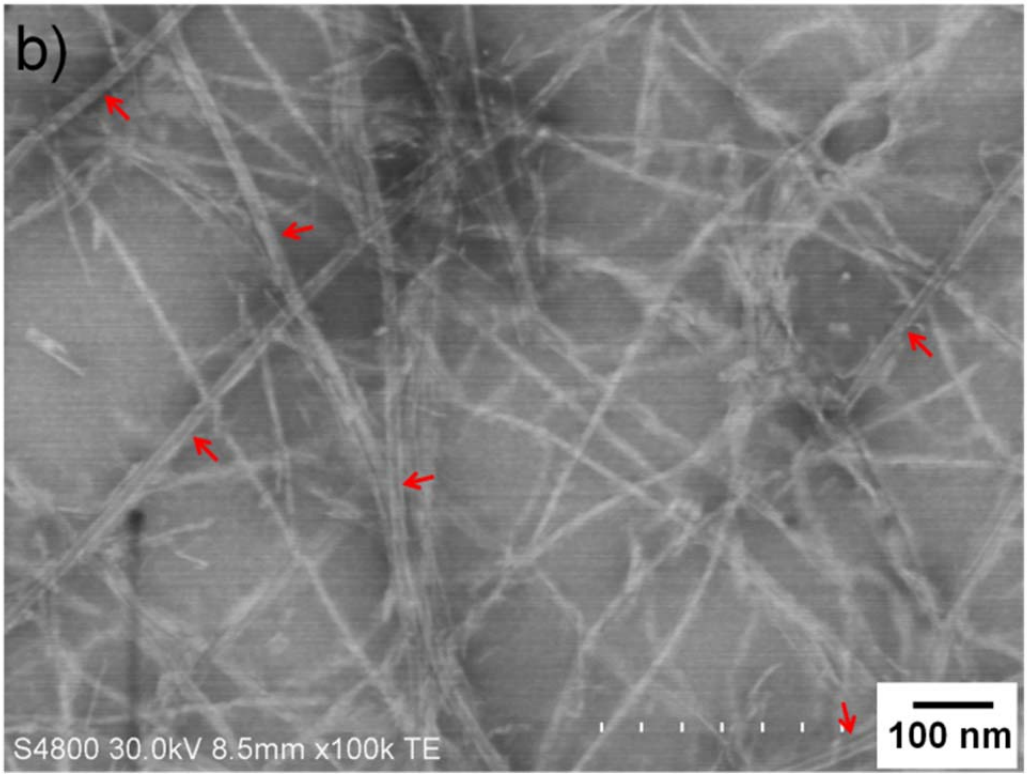

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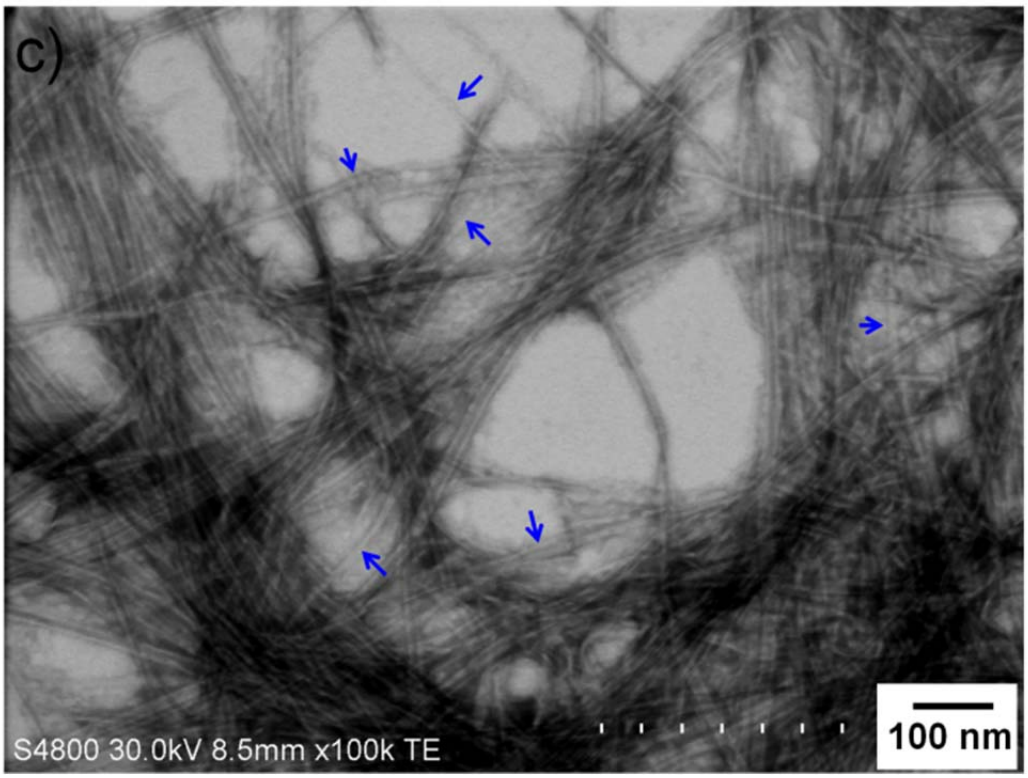

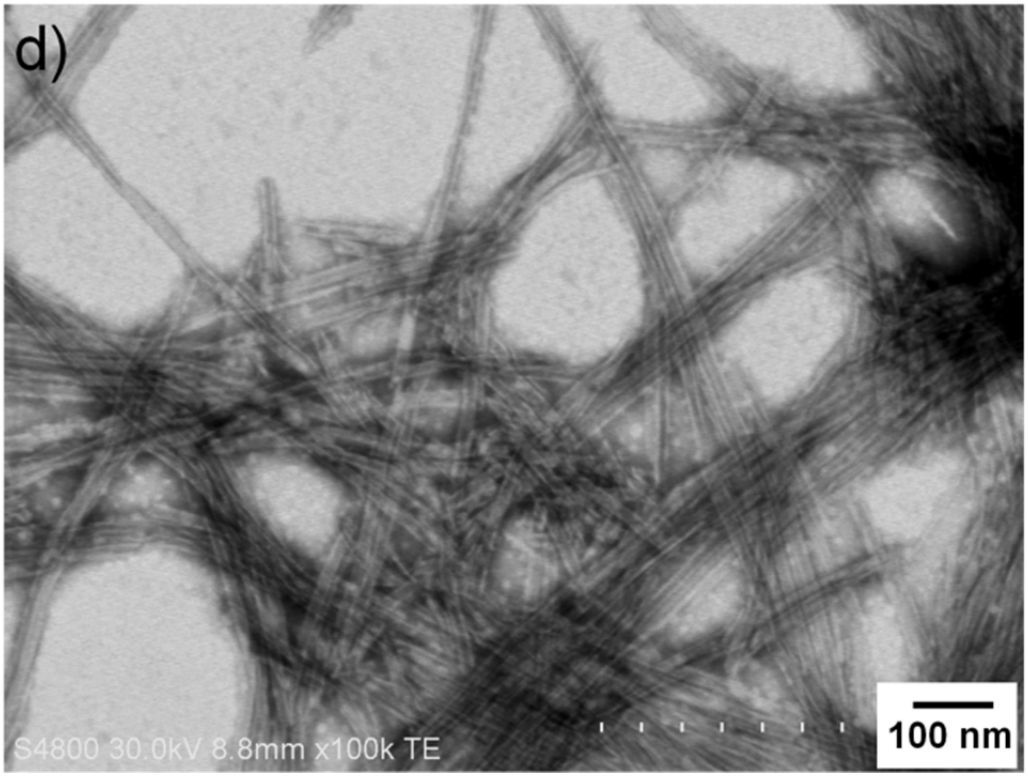

Figure S5 Time-dependent STEM images of mixture solution containing **1**-Na and CDDP (molar ratio of 1/1) upon drying on carbon grids and staining with 2%-phosphotungstate. **a**) 2 h; **b**) 8 h; **c**) 24 h; **d**) 48 h incubation time. Red arrows: ONTs; Blue arrows: Nanofibers.

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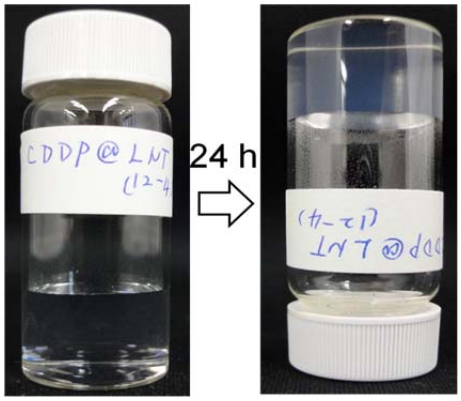

Figure S6 Formation of hydrogel from mixture solution of **1**-Na and CDDP(molar ratio of 1/1) .

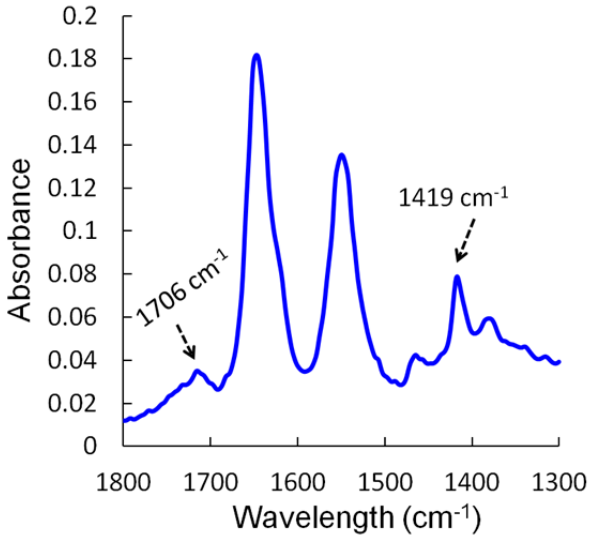

Figure S7 IR spectra of **1** as acidic form. The broad peak around 1706 cm^{-1} is assigned to the $-CO_2H$ group, the peak of 1419 cm^{-1} is assigned to the C–H deformation band of tetraglycines.

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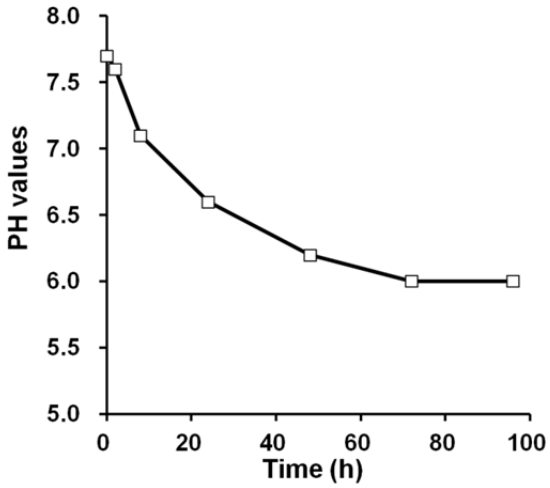

Figure S8 Time dependent pH shift of the mixture solution containing **1**-Na and CDDP (molar ratio of 1/1).

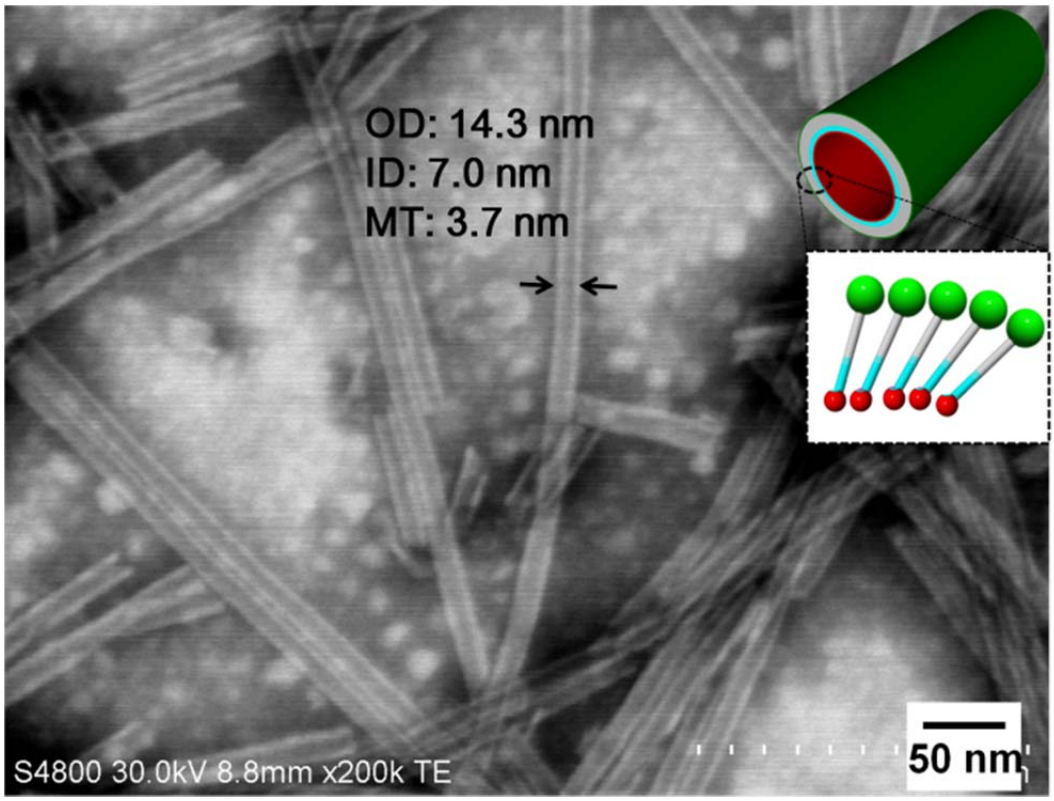

Figure S9 STEM image of bare ONT self-assembled from **1** alone. This bare ONT was prepared from

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the pH adjustment of **1**-Na solution to pH 4. The sample was negatively stained with 2%-phosphotungstate. OD, ID, and MT: outer diameter, inner diameter, and membrane thickness of ONT, respectively. The inset showed the schematic model of bare ONT, which was estimated from the XRD measurement (Figure S10).

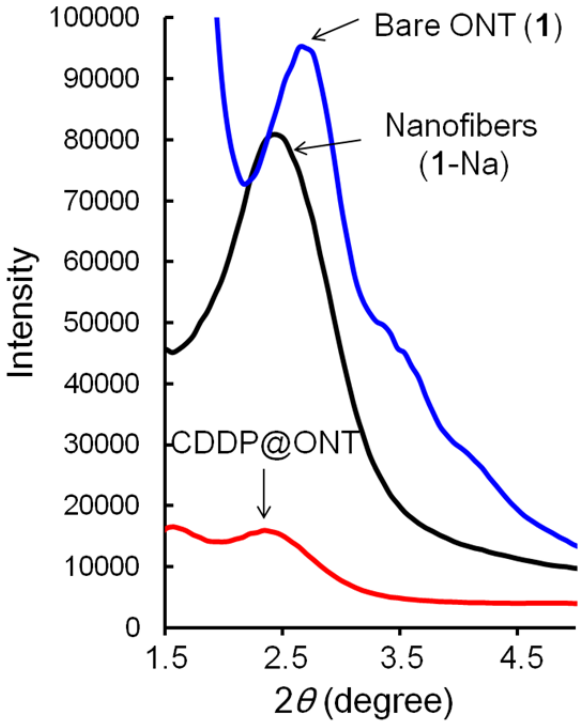

Figure S10 XRD patterns of bare ONT (**1**), nanofibers (**1**-Na), and CDDP@ONT.

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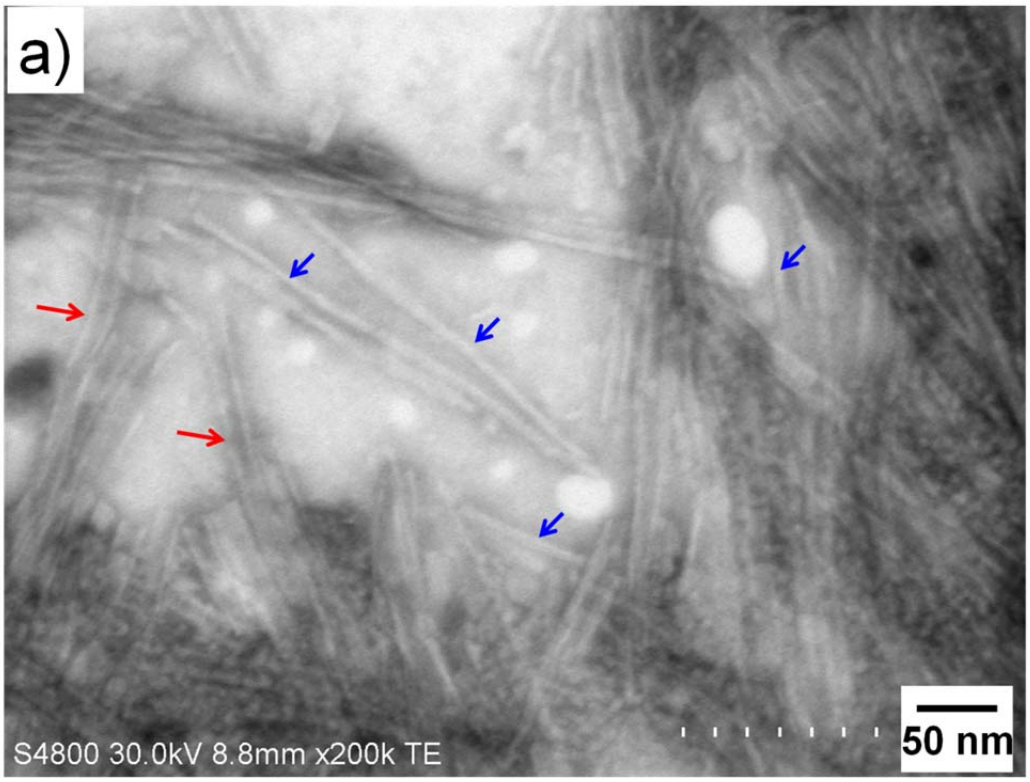

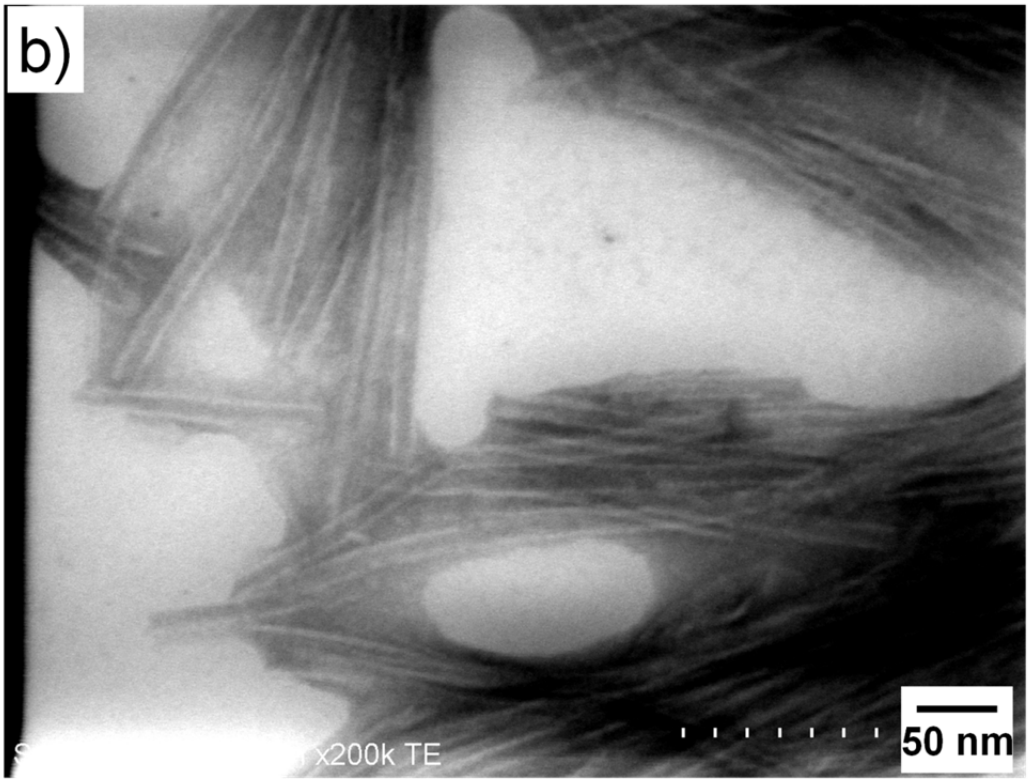

Figure S11 STEM images of CDDP@ONT after the release experiment in **a**) HBS and **b**) HEPES buffer. In **a**) Red arrows: ONTs; Blue arrows: Nanofibers.