Electronic supplementary information

Hydrogen-bonded six-component assembly for capsule formation based on tetra(4-pyridyl)cavitand and isophthalic acid linker and its application to photoresponsive capsule

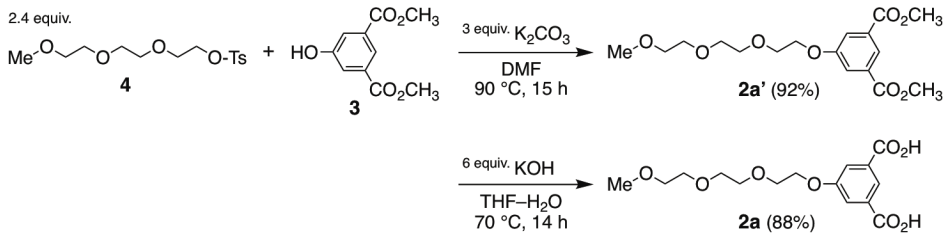
Yuka Togari, Shiori Hirota, Hitomi Kitagawa, Yoshimi Tsukamoto and Kenji Kobayashi*

Department of Chemistry, Faculty of Science, Shizuoka University, 836 Ohya, Suruga-ku, Shizuoka 422-8529, Japan.

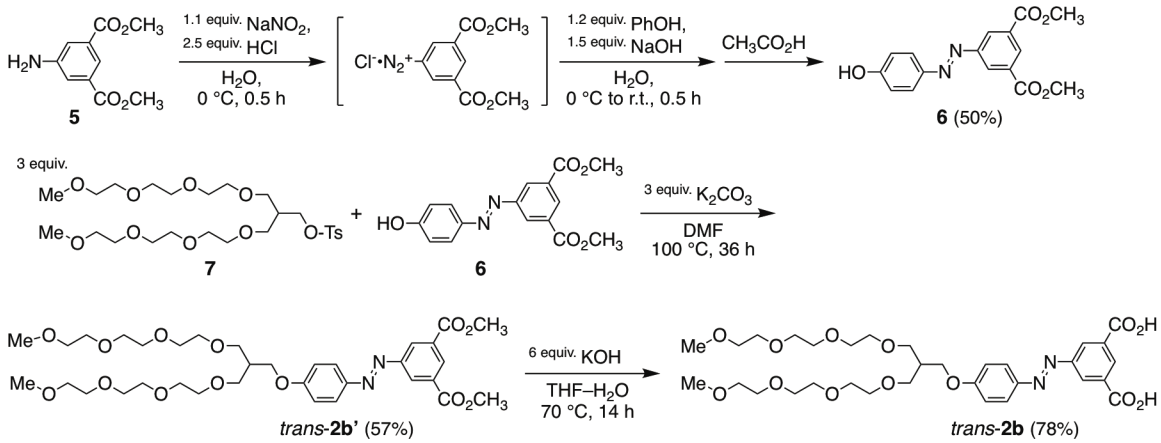
E-mail: kobayashi.kenji.a@shizuoka.ac.jp

Contents

General. DMF was distilled from CaH_2 under an argon atmosphere. The other solvents and all commercially available reagents were used without any purification. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a JEOL JNM-AL400 spectrometer. DOSY NMR spectra were recorded at 600 MHz on a JEOL JNM-ECA600 spectrometer. High resolution FD-TOF-MS measurements were performed on a JEOL JMS-T100GCV. UV–vis absorption spectra were measured on a Shimadzu UV-2450. Photoirradiation was conducted with a 300 W Xe lamp through a color filter for 350 nm or 450 nm light with ASAHI SPECTRA MAX-302. Tetra(4-pyridyl)cavitand **1** was synthesized according to the literature.[1]



Scheme S1 Synthetic route of **2a**.



Scheme S2 Synthetic route of *trans*-**2b**.

Compound 2a′. To a mixture of dimethyl 5-hydroxyisophthalate **3** (4.62 g, 22.0 mmol) and K_2CO_3 (9.11 g, 65.9 mmol) under Ar was added a solution of the tosylate of triethylene glycol monomethyl ether (TEG) **4** (16.9 g, 53.1 mmol) in dry DMF (50 mL). The resulting mixture was stirred at 90 °C for 15 h under Ar. After cooling to room temperature, the reaction mixture was filtered and washed with EtOAc. The filtrate was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O (5 times) and brine and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by column chromatography on silica gel eluted with EtOAc–hexane (1:1) to give **2a′** (7.20 g, 92% yield) as a colorless oil. ^1H NMR ($CDCl_3$) δ 8.29 (s, 1H), 7.78 (d, J = 1.5 Hz, 2H), 4.32 (t, J = 4.4 Hz, 2H), 3.93 (s, 6H), 3.88 (t, J = 4.4 Hz, 2H), 3.77–3.29 (m, 8H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.1, 159.9, 131.8, 123.1, 120.0, 71.9, 70.9, 70.7, 70.6, 69.5, 68.1, 59.0, 52.4; FD-TOF-MS m/z calcd for $C_{17}H_{24}O_8$: 356.1471 $[M]^+$, found: 356.1488.

Compound 2a. To a solution of **2a′** (7.20 g, 20.2 mmol) in THF (50 mL) was added 3 M aq. KOH (40 mL, 120 mmol). The resulting mixture was stirred at 70 °C for 14 h under Ar. After cooling to room temperature and then evaporation of THF, the reaction mixture was acidified to pH = ca. 3 with 2 M aq. HCl at 0 °C. The resulting precipitate was filtered and washed with H_2O and then dried in vacuo to give **2a** (5.85 g, 88% yield) as a white solid. Mp. 128-129 °C; ^1H NMR

(DMSO-d_6) δ 13.3 (s, 2H), 8.06 (t, J = 1.5 Hz, 1H), 7.64 (d, J = 1.5 Hz, 2H), 4.19 (t, J = 4.4 Hz, 2H), 3.76 (t, J = 4.4 Hz, 2H), 3.60–3.39 (m, 8H), 3.21 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.3, 158.6, 132.6, 122.2, 119.1, 71.2, 69.9, 69.7, 69.5, 68.7, 67.8, 58.0; FD-TOF-MS m/z calcd for $C_{15}H_{20}O_8$: 328.1158 $[M]^+$, found: 328.1184.

Dimethyl *trans*-5-(4-hydroxyphenylazo)isophthalate (6). Compound **6** was synthesized by a modified procedure of the literature.[2] To a suspension of dimethyl 5-aminoisophthalate **5** (3.00 g, 14.3 mmol) in H_2O (40 mL) was added 2 M aq. HCl (18 mL). To the resulting solution at 0 °C was added dropwise a solution of $NaNO_2$ (1.09 g, 15.8 mmol) in ice cold H_2O (10 mL) over a period of 10 min. The resulting mixture was stirred at 0 °C for 20 min. To the resulting diazonium salt solution at 0 °C was added dropwise a solution of phenol (1.61 g, 17.1 mmol) in ice cold 3 M aq. NaOH solution (7 mL) over a period of 10 min. The reaction mixture was stirred and allowed to warm up to room temperature for 30 min, and then CH_3CO_2H (1.2 mL, 21 mmol) was added to the the reaction mixture at 0 °C. The resulting precipitate was filtered and washed with H_2O and then dried in vacuo to give **6** (2.25 g, 50% yield) as an orange solid. Mp. 215-216 °C; ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 8.48 (d, J = 1.5 Hz, 2H), 8.47 (t, J = 1.5 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.92 (s, 6H); ^{13}C NMR (DMSO-d_6) d 164.9, 161.9, 152.3, 145.0, 131.5, 130.4, 126.3, 125.5, 116.1, 52.7.

Compound *trans*-2b′. To a mixture of **6** (1.34 g, 4.26 mmol) and K_2CO_3 (1.77 g, 12.8 mmol) under Ar was added a solution of the tosylate of the two dichotomous branching TEG groups **7**[3] (7.06 g, 12.8 mmol) in dry DMF (50 mL). The resulting mixture was stirred at 100 °C for 36 h under Ar and light shielding. After cooling to room temperature, the reaction mixture was filtered and washed with EtOAc. The filtrate was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O (5 times) and brine and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by column chromatography on silica gel eluted with EtOAc and then EtOAc–MeOH (100:1) to give *trans*-**2b′** (1.68 g, 57% yield) as an orange viscous oil. ^{1}H NMR ($CDCl_3$) δ 8.76 (t, J = 1.5 Hz, 1H), 8.71 (d, J = 1.5 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 4.16 (d, J = 5.9 Hz, 2H), 4.01 (s, 6H), 3.67-3.63 (m, 24H), 3.55-3.53 (m, 4H), 3.38 (s, 6H), 2.48-2.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 165.9, 162.4, 152.9, 146.6, 131.6, 127.5, 125.3, 114.9, 71.9, 70.68, 70.65, 70.63, 70.54, 70.51, 69.2, 66.5, 59.1, 52.6, 39.9; FD-TOF-MS m/z calcd for $C_{34}H_{50}N_2O_{13}$: 694.3313 $[M]^+$, found: 694.3334.

Compound *trans*-2b. To a solution of **2a′** (980 mg, 1.41 mmol) in THF (30 mL) was added 3 M aq. KOH (3 mL, 9 mmol). The resulting mixture was stirred at 70 °C for 14 h under Ar and light shielding. After cooling to room temperature and then evaporation of THF, the reaction mixture was acidified to pH = ca. 3 with 2 M aq. HCl at 0 °C. The resulting precipitate was filtered and washed with H_2O and then dried in vacuo to give *trans*-**2b** (733 mg, 78% yield) as an orange viscous solid. ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.56 (s, 2H), 7.70 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.14-4.12 (m, 2H), 3.69-3.65 (m, 24H), 3.58-3.56 (m, 4H), 3.39 (s, 6H), 2.50-2.47 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 169.4, 162.6, 153.0, 146.8, 132.8, 131.8, 128.7, 125.7, 115.2, 72.3, 71.02, 71.00, 70.94, 70.89, 69.7, 66.7, 59.4, 40.2; FD-TOF-MS m/z calcd for $C_{32}H_{46}N_2O_{13}$: 666.3000 $[M]^+$, found: 666.3029.

References

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3 T. Sakano, T. Ohashi, M. Yamanaka and K. Kobayashi, *Org. Biomol. Chem.*, 2015, **13**, 8359-8364.

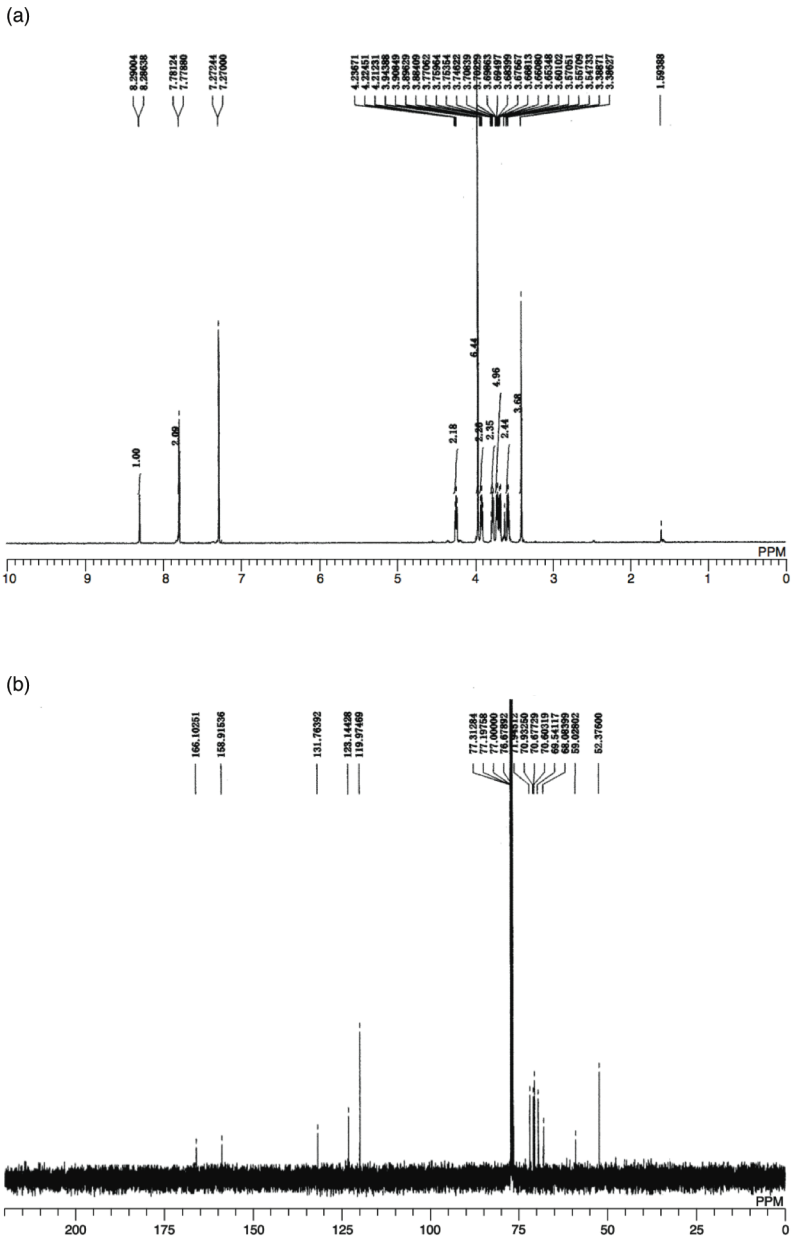


Fig. S1 (a) ^{1}H NMR and (b) ^{13}C NMR spectra of **2a′** in $CDCl_3$.

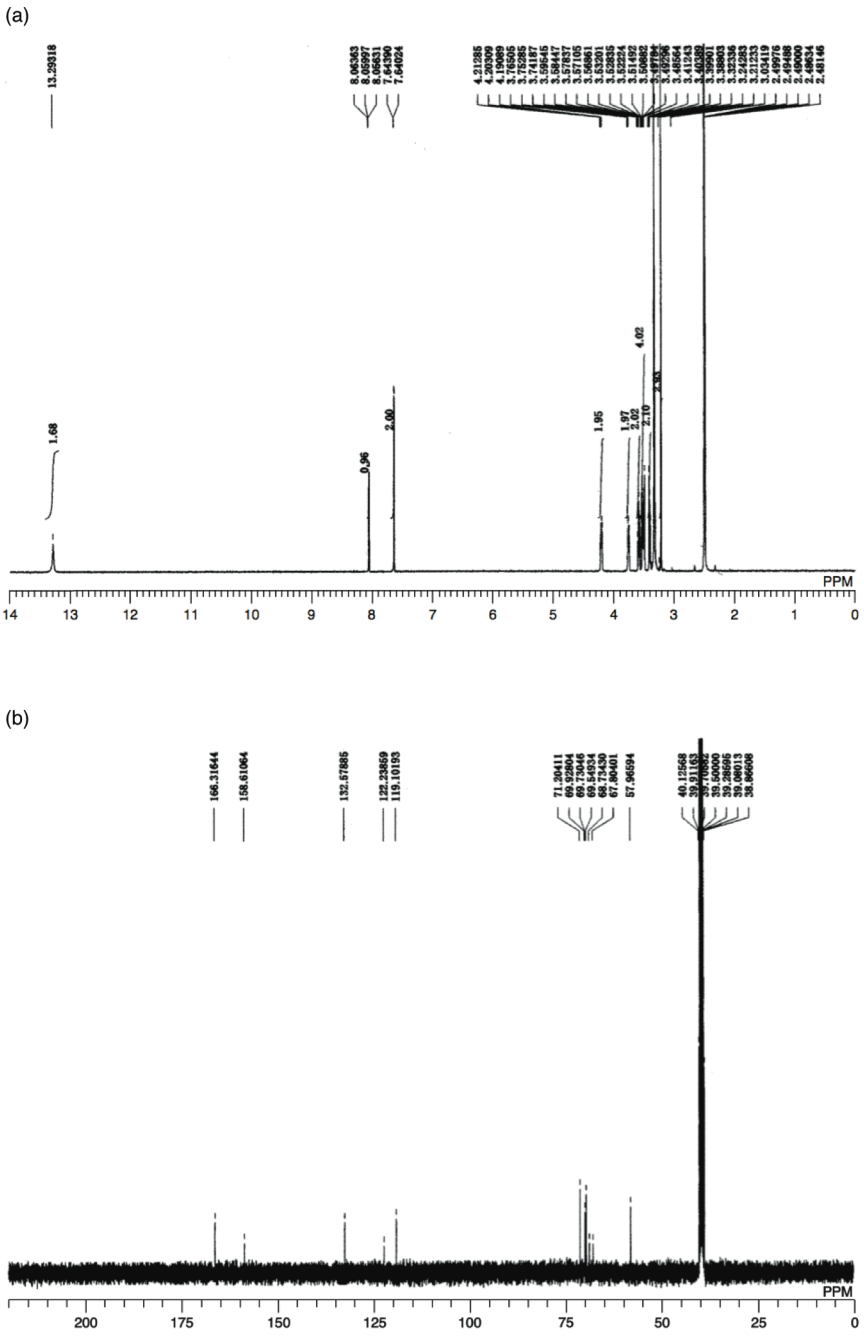


Fig. S2 (a) ^{1}H NMR and (b) ^{13}C NMR spectra of **2a** in DMSO-d_6.

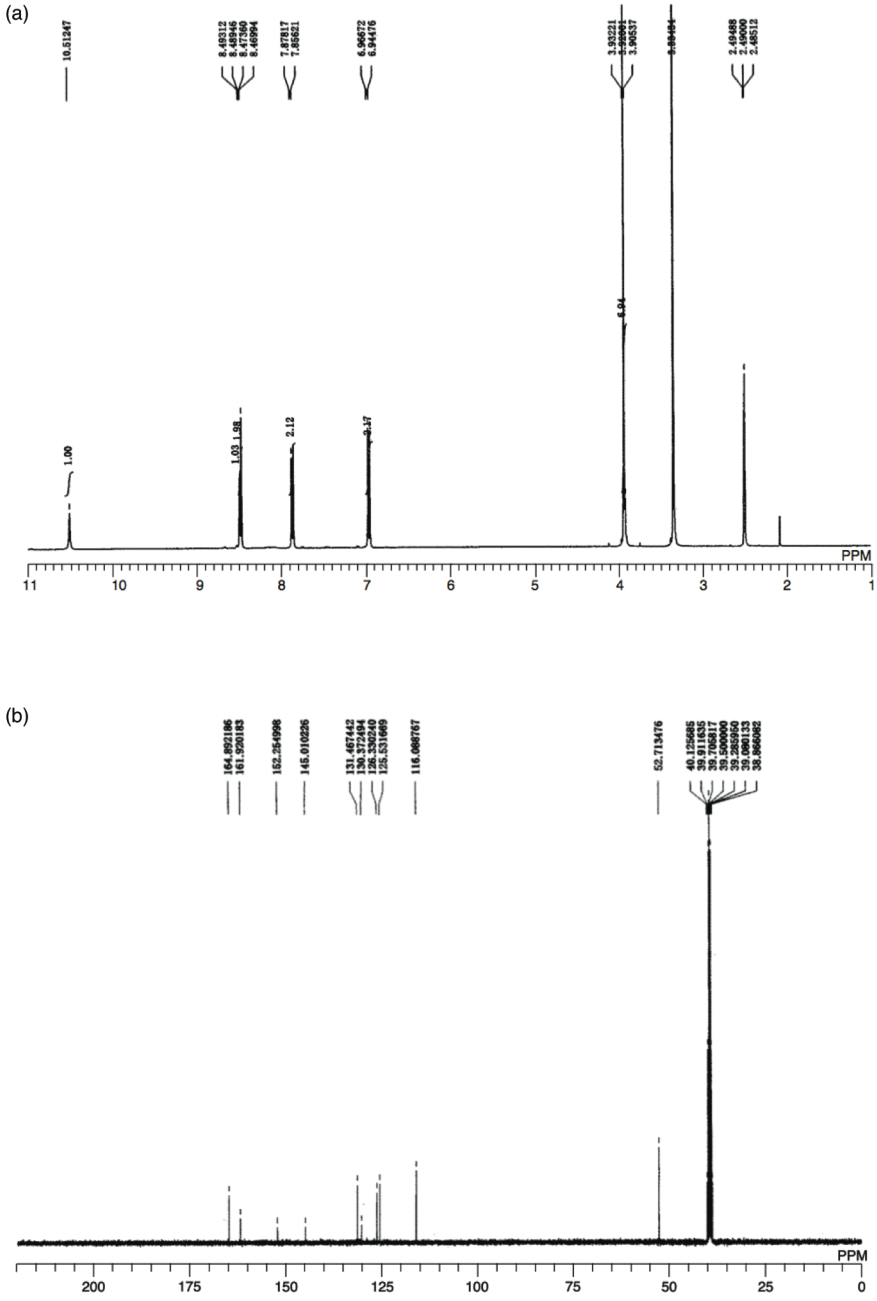


Fig. S3 (a) ^{1}H NMR and (b) ^{13}C NMR spectra of **6** in DMSO-d_6.

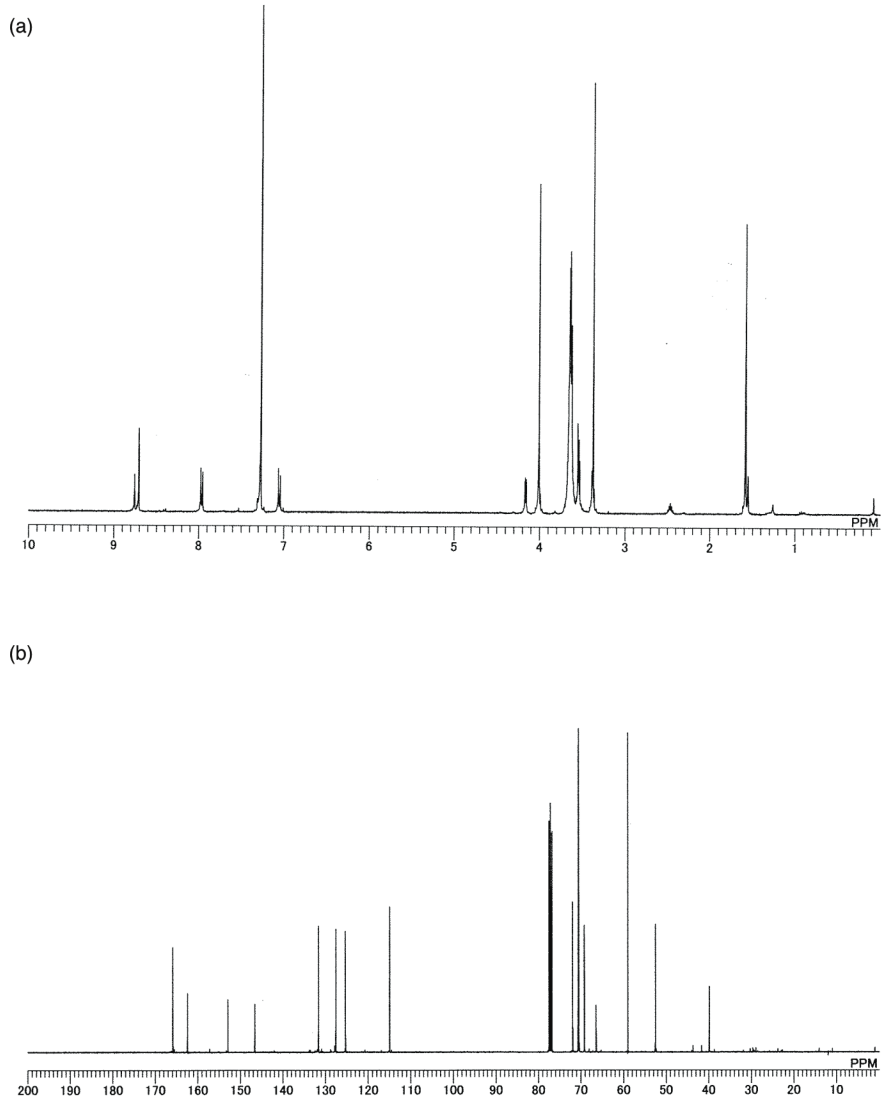


Fig. S4 (a) ^{1}H NMR and (b) ^{13}C NMR spectra of *trans*-**2b′** in $CDCl_3$.

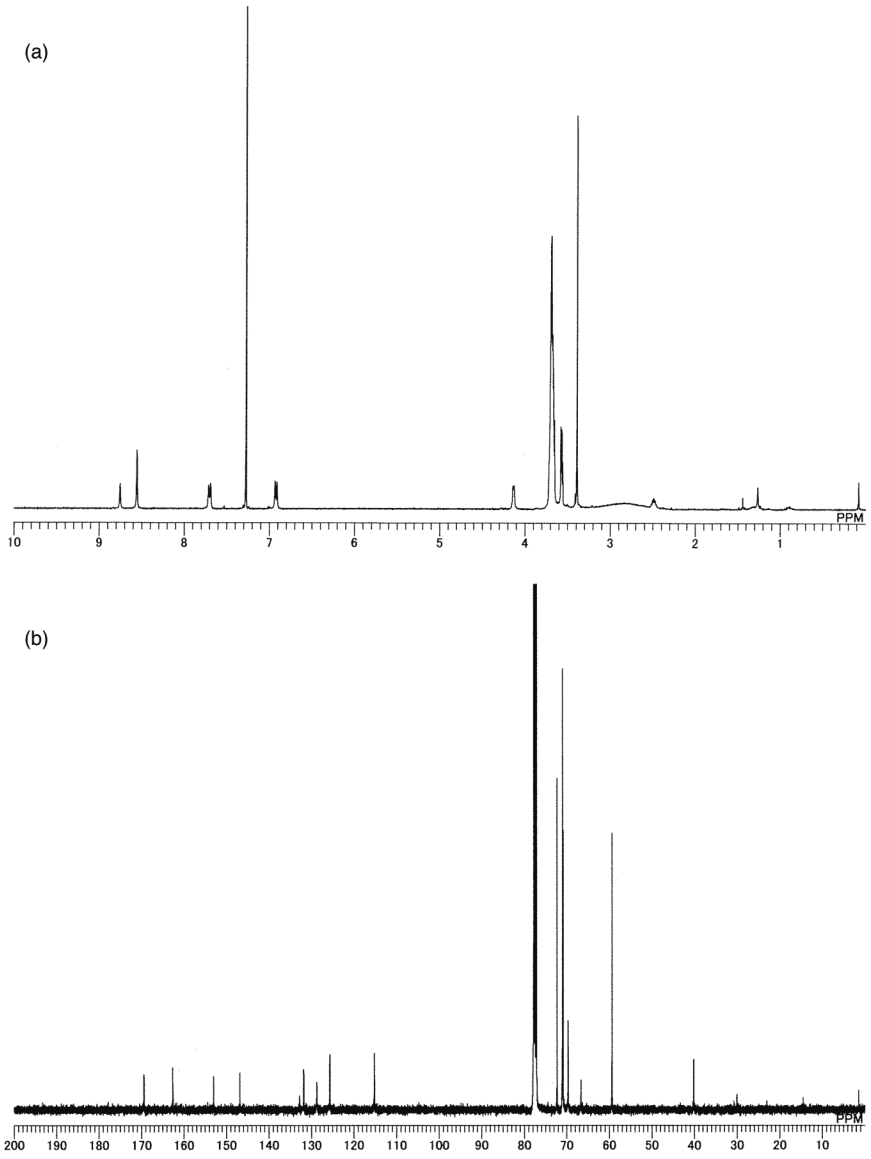
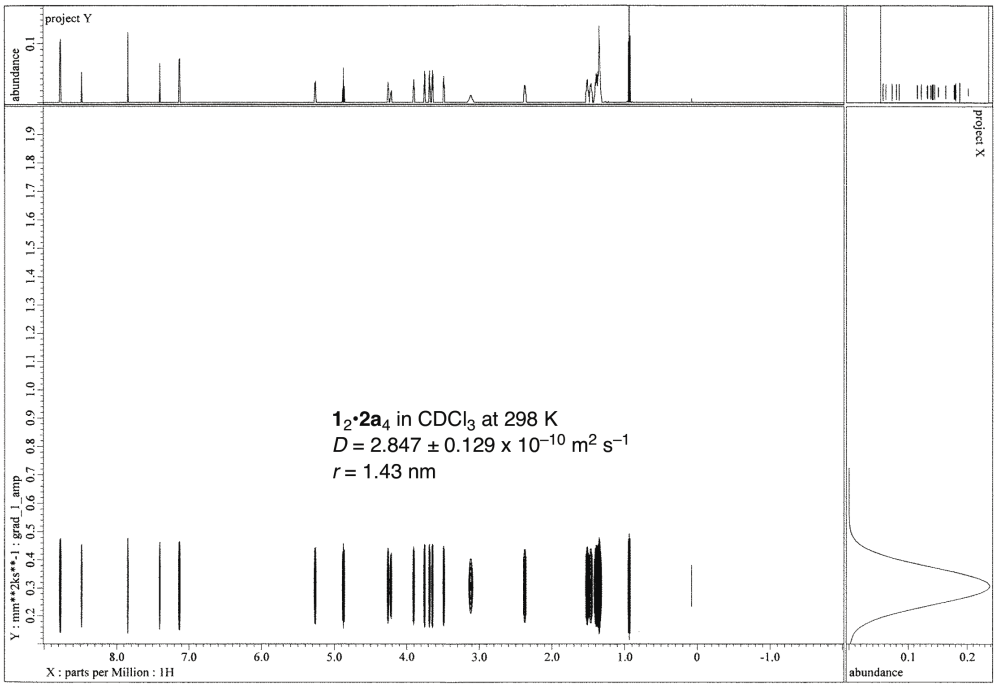


Fig. S5 (a) ^{1}H NMR and (b) ^{13}C NMR spectra of *trans*-**2b** in $CDCl_3$.

(a)



(b)

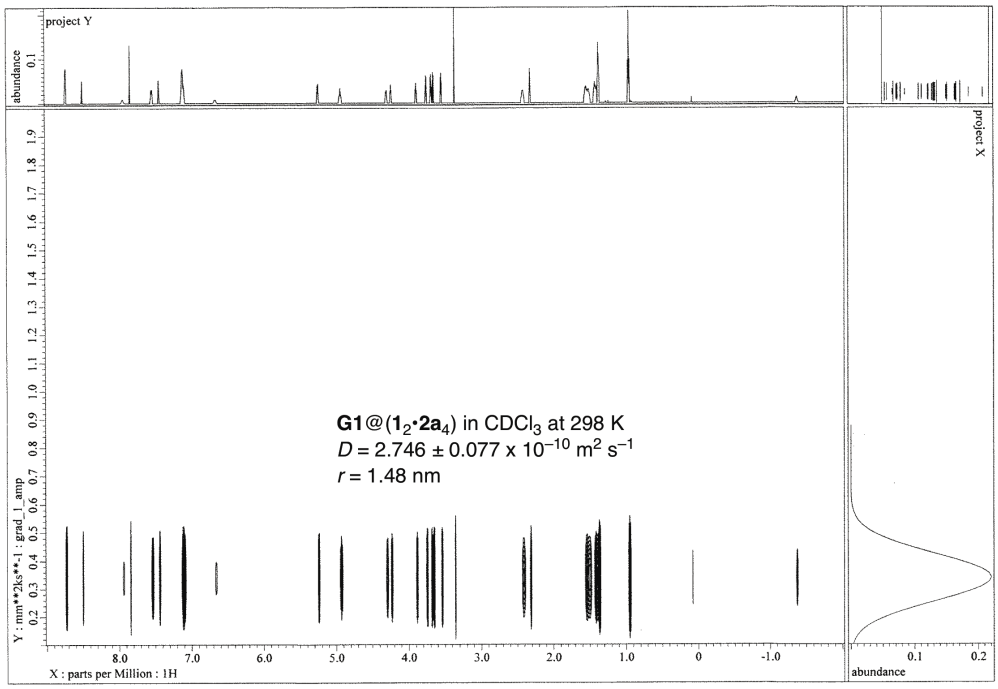


Fig. S6 DOSY NMR spectra (600 MHz) of (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM: [**1**] = 4 mM and [**2a**] = 8 mM) and (b) **G1**@($\mathbf{1}_2$•$\mathbf{2a}_4$) (2 mM: [**1**] = 4 mM, [**2a**] = 8 mM, and [**G1**] = 6 mM) in $CDCl_3$ at 298 K. Diffusion time = 200 ms. Grad 1 = 1.1 ms. Grad 1 amp = 0.010 ~ 0.290 T/m, 16 points. Relaxation delay = 7 s.

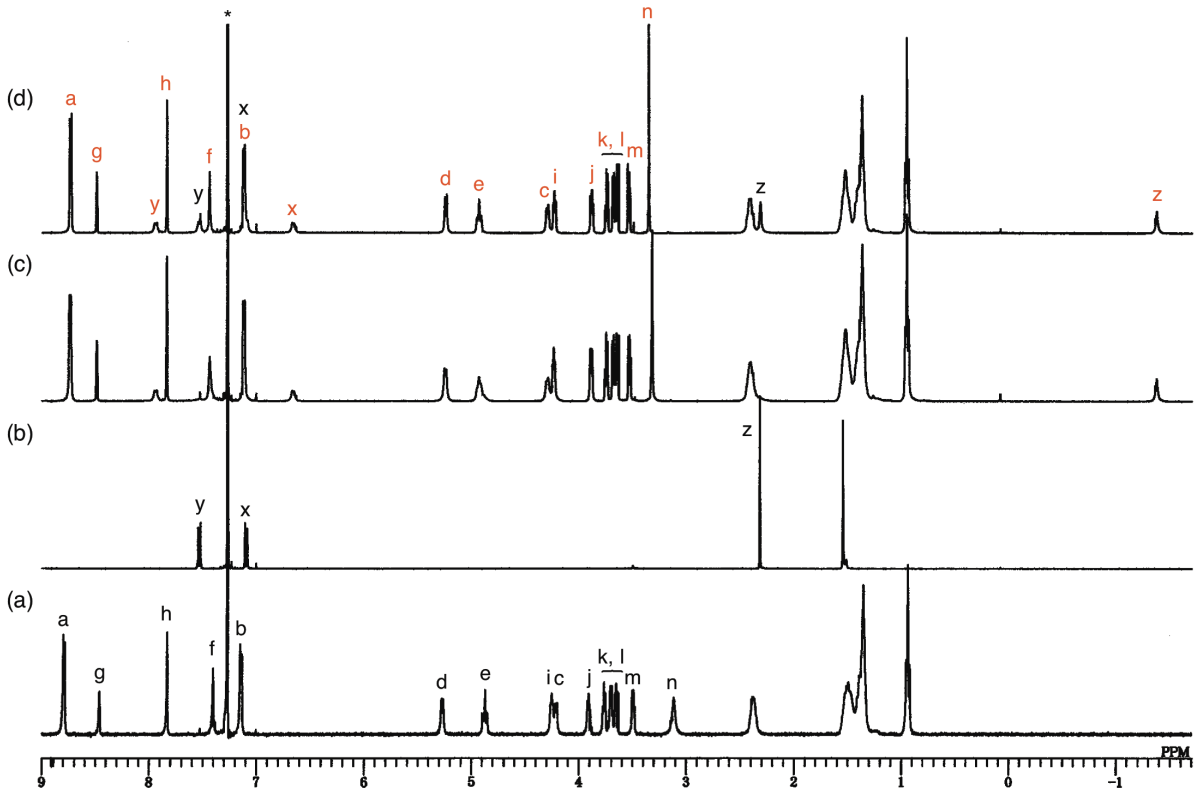


Fig. S7 Association behavior of self-assembled capsule $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) with guest **G1**, monitored by ^{1}H NMR ($CDCl_3$, 298 K): (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ alone, (b) **G1** alone, (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (1 equiv), and (d) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (2 equiv). The marked signals are assigned in Scheme 1a,c. The representative signals of free **G1** and guest-free $\mathbf{1}_2$•$\mathbf{2a}_4$ are shown in black, and the representative signals of **G1**@($\mathbf{1}_2$•$\mathbf{2a}_4$) are shown in red. The asterisk is the residual solvent signal.

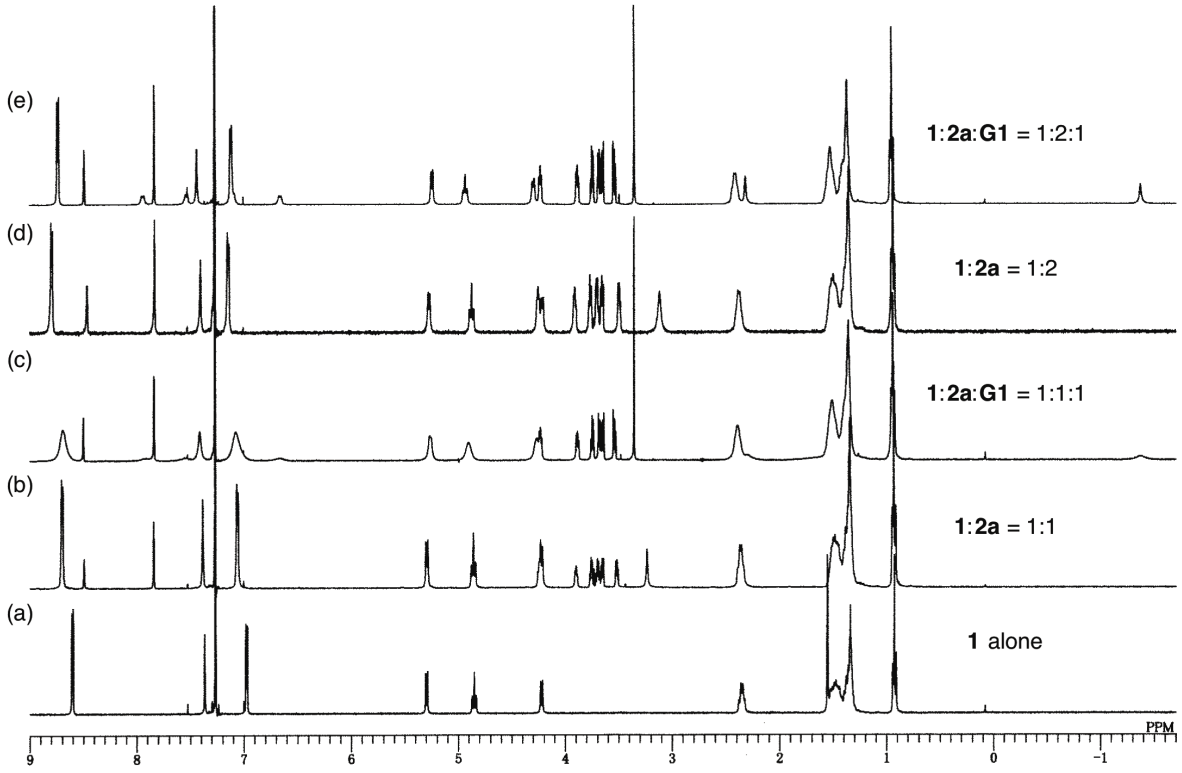


Fig. S8 Association behavior of a mixture of **1**, **2a**, and **G1** in various ratios, monitored by ^{1}H NMR ($CDCl_3$, 298 K): (a) **1** alone, (b) [**1**] = 4 mM and [**2a**] = 4 mM, (c) [**1**] = 4 mM, [**2a**] = 4 mM, and [**G1**] = 4 mM, (d) [**1**] = 4 mM and [**2a**] = 8 mM ([$\mathbf{1}_2$•$\mathbf{2a}_4$] = 2 mM), and (e) [**1**] = 4 mM, [**2a**] = 8 mM, and [**G1**] = 4 mM (**G1**@($\mathbf{1}_2$•$\mathbf{2a}_4$) + **G1**).

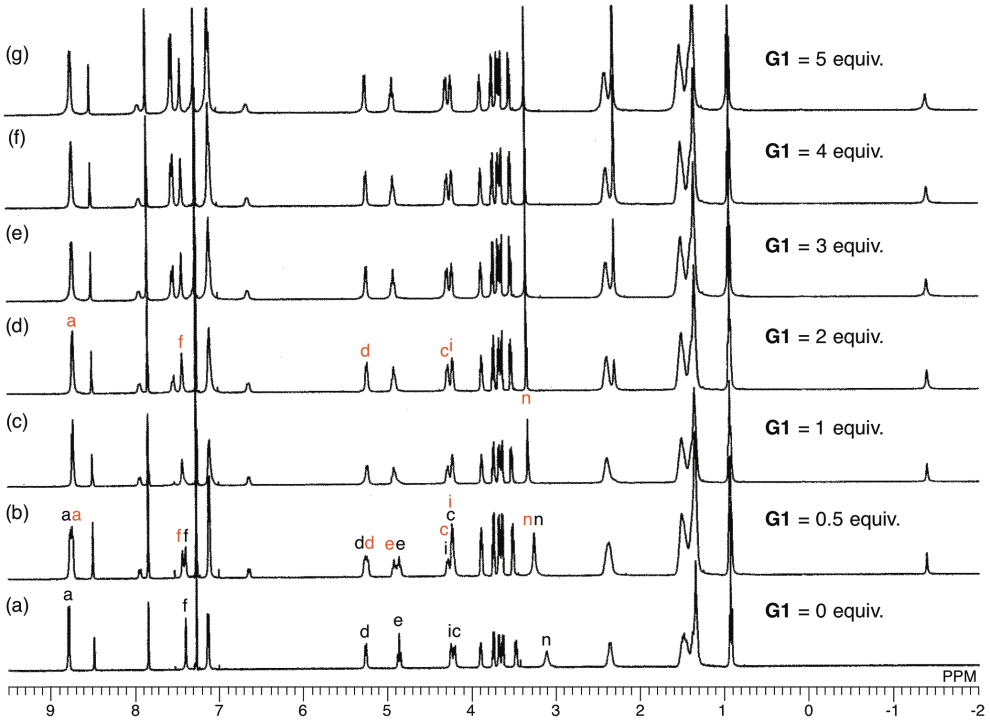


Fig. S9 Association behavior of self-assembled capsule $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) with guest **G1** in various ratios, monitored by ^{1}H NMR ($CDCl_3$, 298 K): (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ alone, (b) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (0.5 equiv), (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (1 equiv), (d) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (2 equiv), (e) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (3 equiv), (f) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (4 equiv), and (g) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G1** (5 equiv). The marked signals are assigned in Scheme 1a,c. The representative signals of guest-free $\mathbf{1}_2$•$\mathbf{2a}_4$ and **G1**@($\mathbf{1}_2$•$\mathbf{2a}_4$) are shown in black and red, respectively.

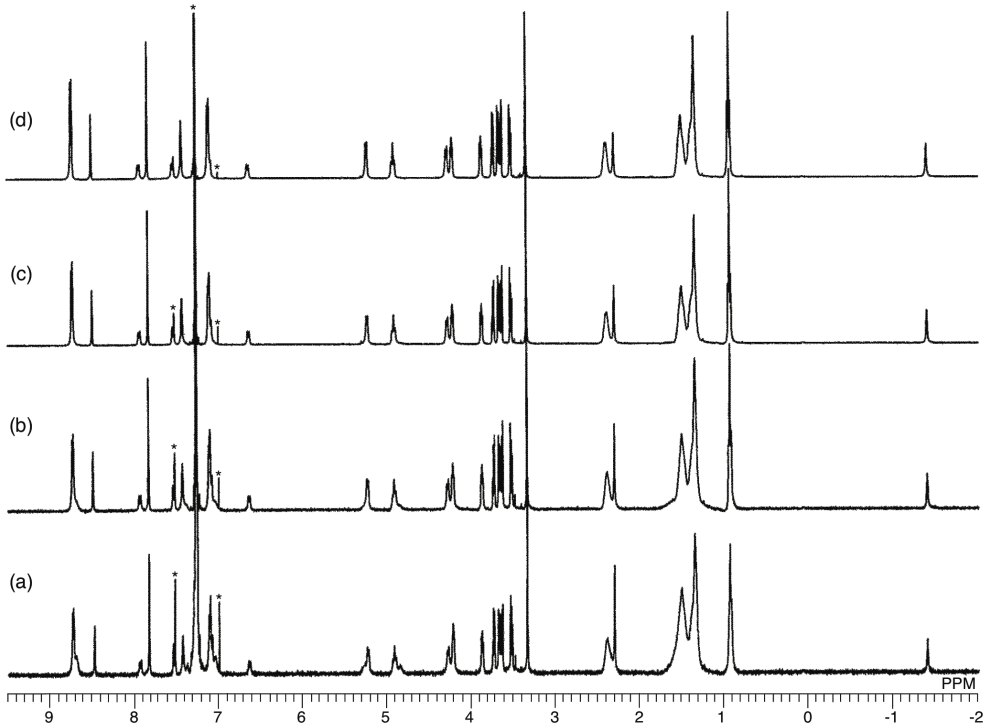


Fig. S10 Dilution experiments of **G1**@($\mathbf{1}_2$•$\mathbf{2a}_4$) (2–0.25 mM), monitored by ^{1}H NMR ($CDCl_3$, 298 K), wherein **1**:**2a**:**G1** ratio is constant with 1:2:1: (a) [**1**] = 0.5 mM, [**2a**] = 1 mM, and [**G1**] = 0.5 mM, (b) [**1**] = 1 mM, [**2a**] = 2 mM, and [**G1**] = 1 mM, (c) [**1**] = 2 mM, [**2a**] = 4 mM, and [**G1**] = 2 mM, and (d) [**1**] = 4 mM, [**2a**] = 8 mM, and [**G1**] = 4 mM. Asterisks are the residual solvent signal and its satellite signal.

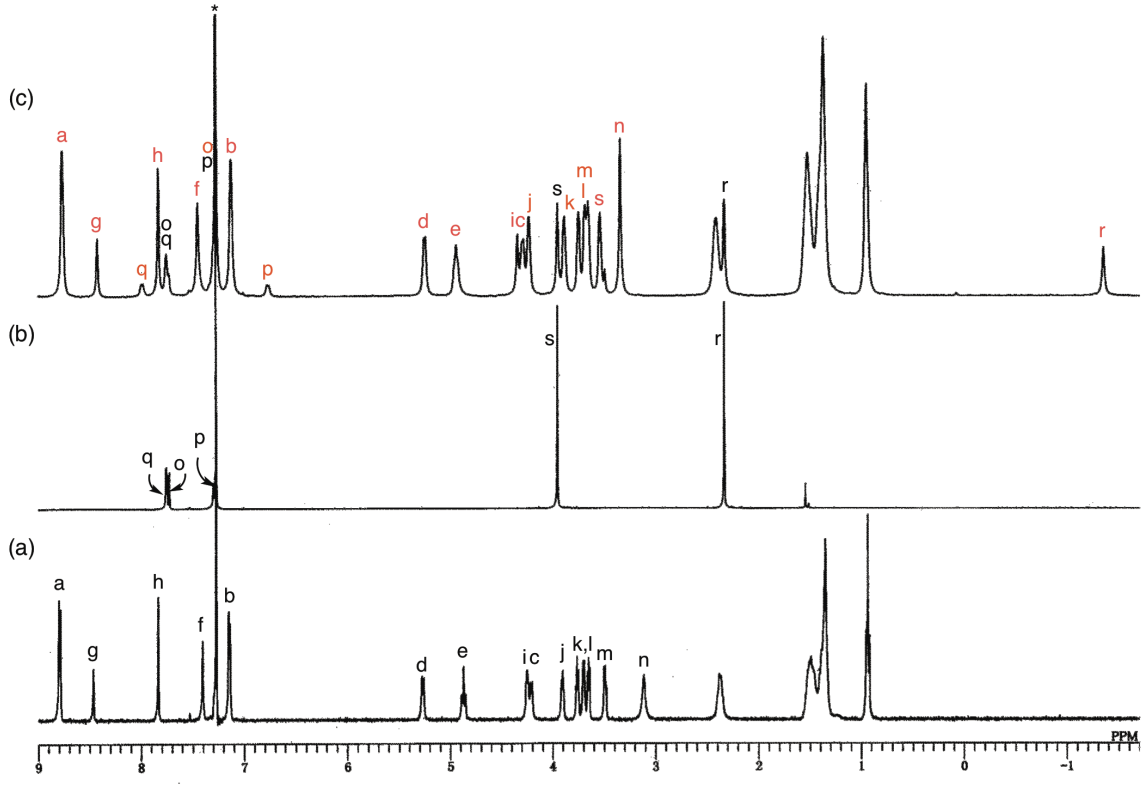


Fig. S11 Association behavior of self-assembled capsule $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) with guest **G2**, monitored by ^{1}H NMR ($CDCl_3$, 298 K): (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ alone, (b) **G2** alone, and (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G2** (2 equiv). The marked signals are assigned in Scheme 1a,c. The representative signals of free **G2** and guest-free $\mathbf{1}_2$•$\mathbf{2a}_4$ are shown in black, and the representative signals of **G2**@($\mathbf{1}_2$•$\mathbf{2a}_4$) are shown in red. The asterisk is the residual solvent signal.

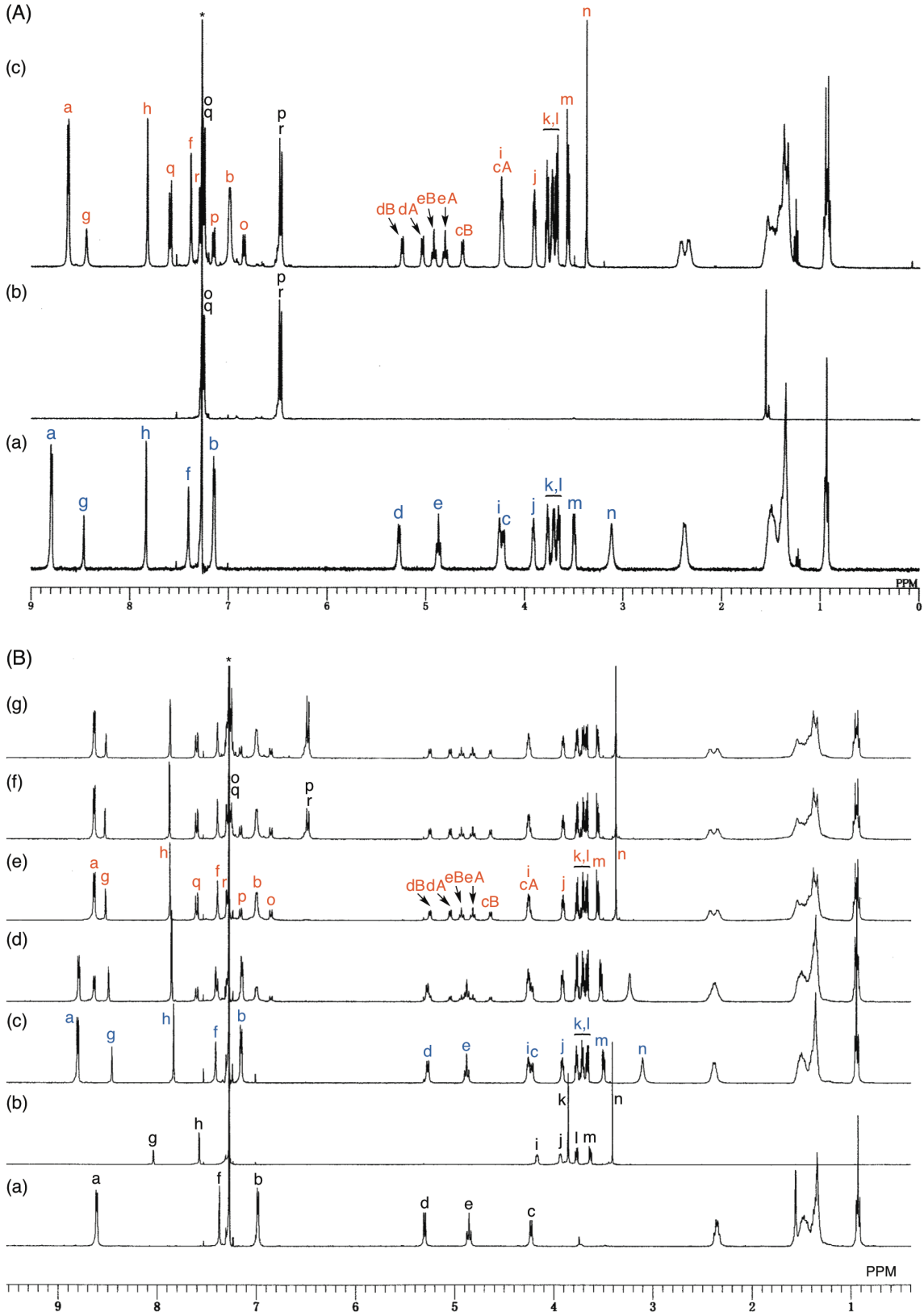


Fig. S12 Association behavior of self-assembled capsule $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) with guest **G3**, monitored by ^{1}H NMR ($CDCl_3$, 298 K).
(A) (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ alone, (b) **G3** alone, and (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G3** (2 equiv). The marked signals are assigned in Scheme 1a,c and Fig. 4. The representative signals of free **G3** and guest-free $\mathbf{1}_2$•$\mathbf{2a}_4$ are shown in black and blue, respectively, and the representative signals of **G3**@($\mathbf{1}_2$•$\mathbf{2a}_4$) are shown in red. The asterisk is the residual solvent signal.
(B) (a) **1** alone, (b) **2a** alone, (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ alone, (d) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G3** (0.5 equiv), (e) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G3** (1 equiv), (f) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G3** (2 equiv), and (g) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G3** (3 equiv). The representative signals of free **1** and free **2a** are also shown in black.

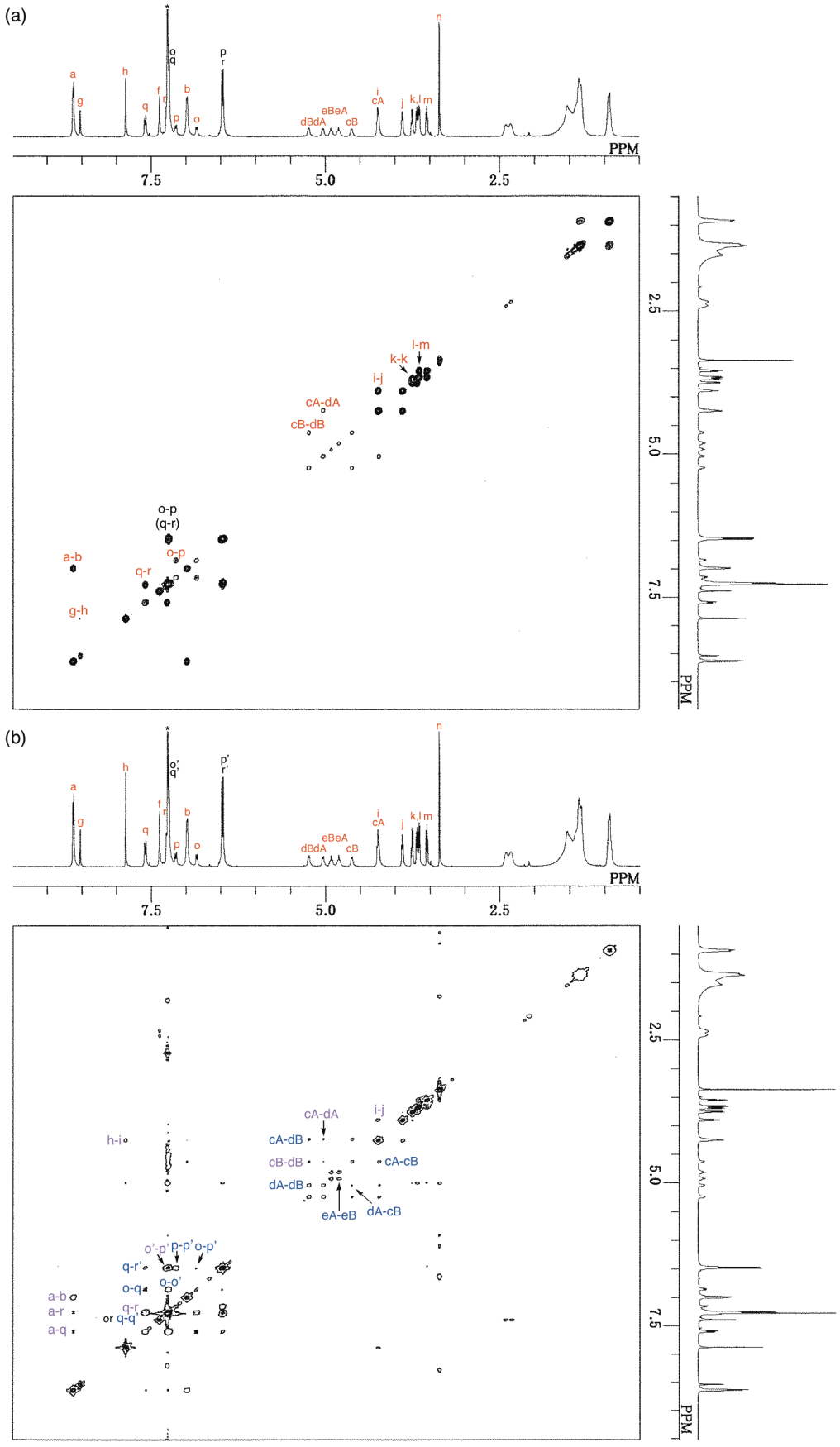


Fig. S13 (a) ^{1}H–^{1}H COSY spectrum of a mixture of $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G3** (4 mM) in $CDCl_3$ at 298 K. The representative signals of free **G3** and **G3**@($\mathbf{1}_2$•$\mathbf{2a}_4$) are shown in black and red, respectively.
(b) 2D NOESY spectrum (mixing time = 0.4 s and pulse delay = 1.5 s) of a mixture of $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G3** (4 mM) in $CDCl_3$ at 298 K. Assignments of NOE correlations and exchange cross-peaks are shown in purple and blue, respectively.

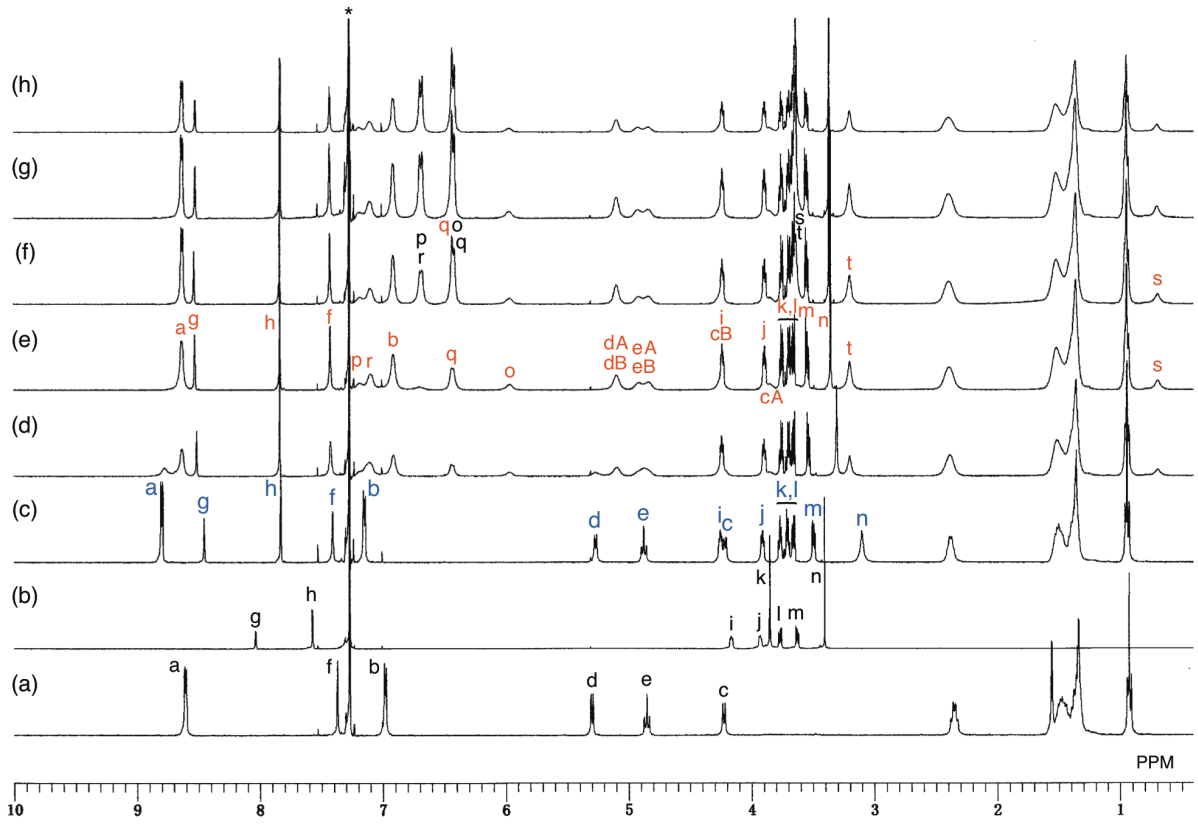


Fig. S14 Association behavior of self-assembled capsule $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) with guest **G4**, monitored by ^{1}H NMR ($CDCl_3$, 298 K): (a) **1** alone, (b) **2a** alone, (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ alone, (d) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G4** (0.5 equiv), (e) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G4** (1 equiv), (f) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G4** (2 equiv), and (g) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G4** (3 equiv); (h) $\mathbf{1}_2$•$\mathbf{2a}_4$ + **G4** (3 equiv) after heating 50 °C for 24 h. The marked signals are assigned in Scheme 1a,c (see also Fig. 4). The representative signals of free **G4** and guest-free $\mathbf{1}_2$•$\mathbf{2a}_4$ are shown in black and blue, respectively, and the representative signals of **G4**@($\mathbf{1}_2$•$\mathbf{2a}_4$) are shown in red. The representative signals of free **1** and free **2a** are also shown in black. The asterisk is the residual solvent signal.

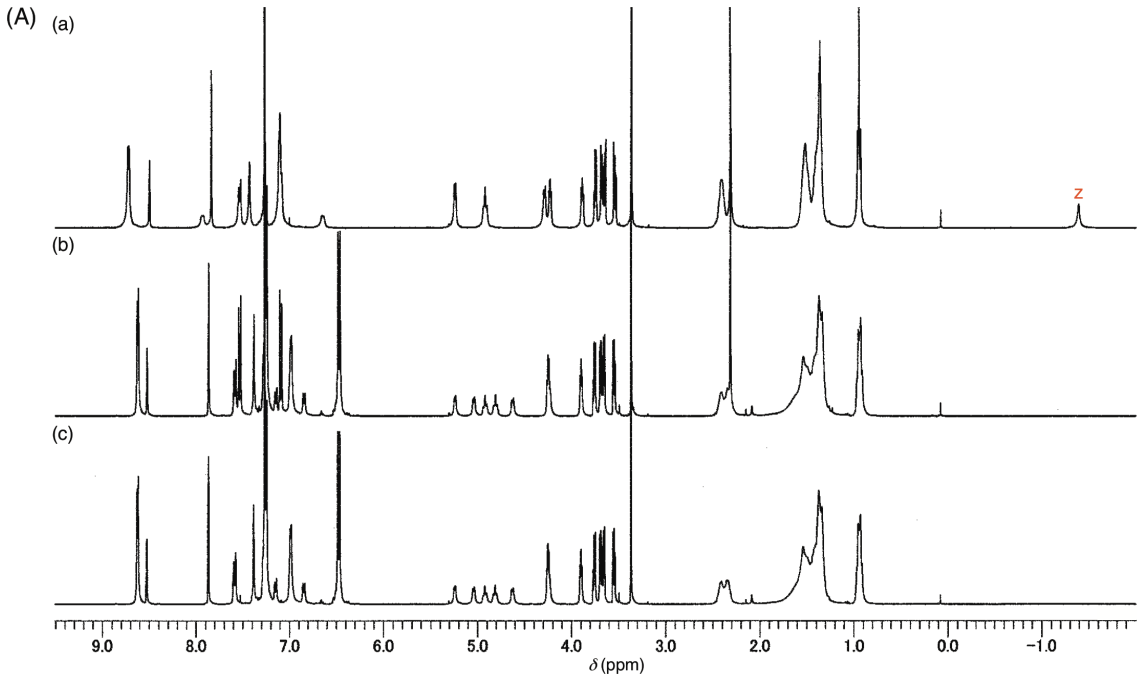


Fig. S15 ^{1}H NMR spectra ($CDCl_3$, 298 K) for the competitive guest-encapsulation experiments of $\mathbf{1}_2$•$\mathbf{2a}_4$.
(A) (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G1** (6 mM) (**G1**@($\mathbf{1}_2$•$\mathbf{2a}_4$) and free **G1**), (b) a mixture of $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM), **G1** (6 mM), and **G3** (4 mM), and (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G3** (4 mM) (**G3**@($\mathbf{1}_2$•$\mathbf{2a}_4$) and free **G3**).

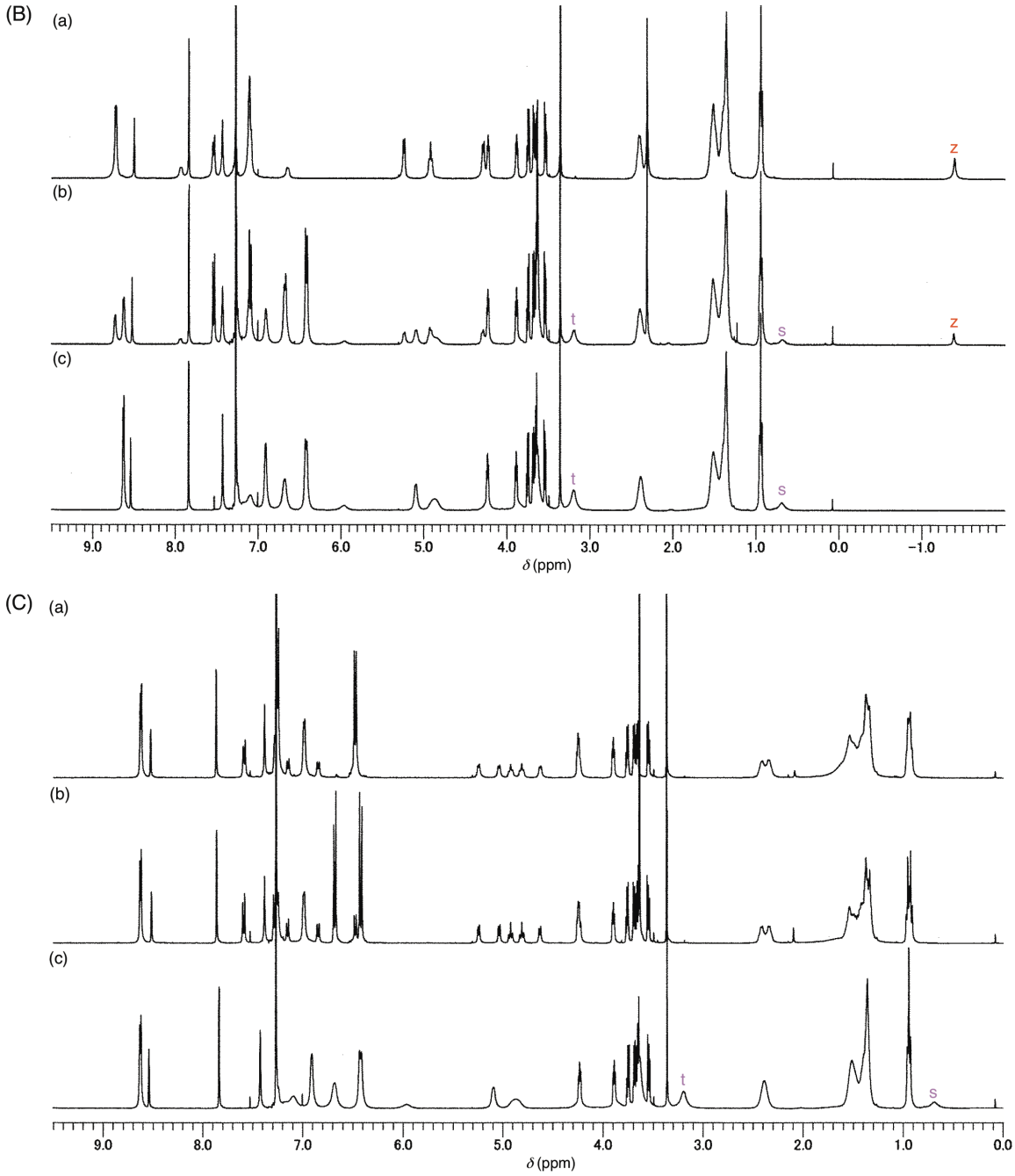


Fig. S15 (continued) ^{1}H NMR spectra ($CDCl_3$, 298 K) for the competitive guest-encapsulation experiments of $\mathbf{1}_2$•$\mathbf{2a}_4$. (B) (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G1** (6 mM) (**G1**@($\mathbf{1}_2$•$\mathbf{2a}_4$) and free **G1**), (b) a mixture of $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM), **G1** (6 mM), and **G4** (4 mM), and (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G4** (4 mM) (**G4**@($\mathbf{1}_2$•$\mathbf{2a}_4$) and free **G4**).
(C) (a) $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G3** (4 mM) (**G3**@($\mathbf{1}_2$•$\mathbf{2a}_4$) and free **G3**), (b) a mixture of $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM), **G3** (4 mM), and **G4** (4 mM), and (c) $\mathbf{1}_2$•$\mathbf{2a}_4$ (2 mM) and **G4** (4 mM) (**G4**@($\mathbf{1}_2$•$\mathbf{2a}_4$) and free **G4**).

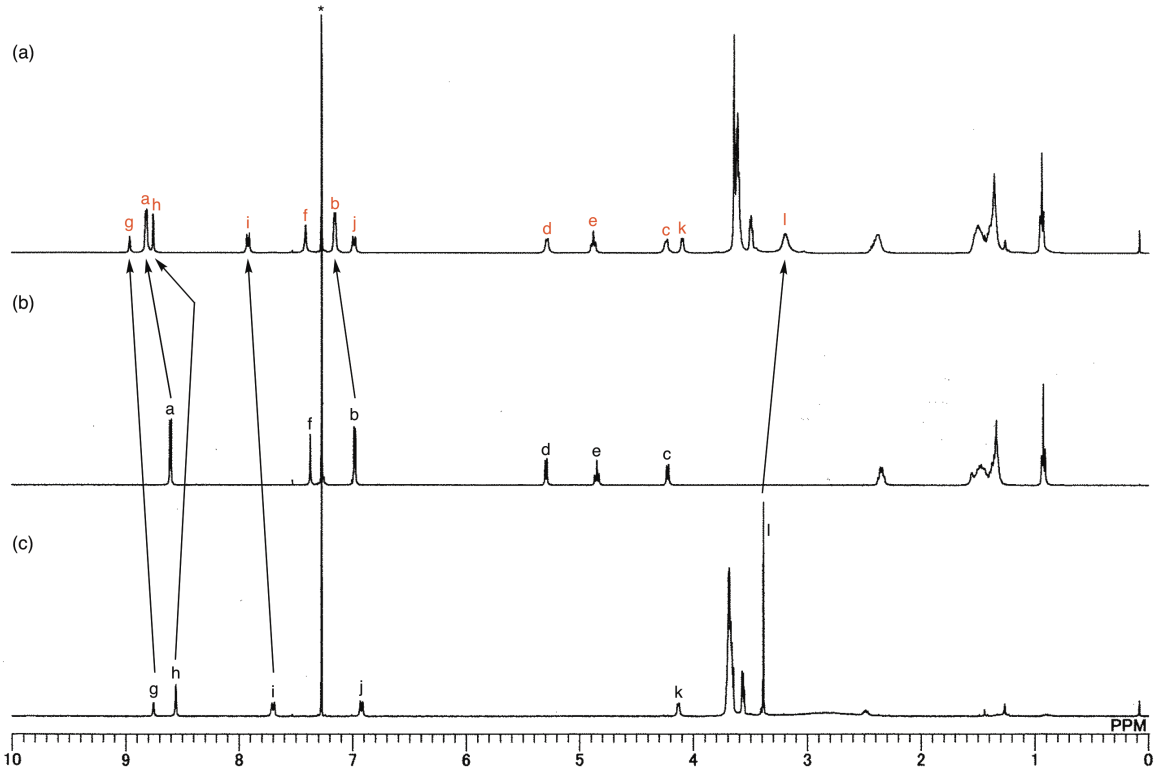


Fig. S16 ^{1}H NMR spectra ($CDCl_3$, 298 K) of (a) self-assembled capsule $\mathbf{1}_2$•(*trans*-**2b**)$_4$ ([**1**] = 4 mM and [*trans*-**2b**] = 8 mM), (b) **1** alone, and (c) *trans*-**2b** alone. The signals marked a–*l* are assigned in Scheme 2a. The representative signals of free species and capsule $\mathbf{1}_2$•(*trans*-**2b**)$_4$ are shown in black and red, respectively. Asterisk is the residual solvent signal.

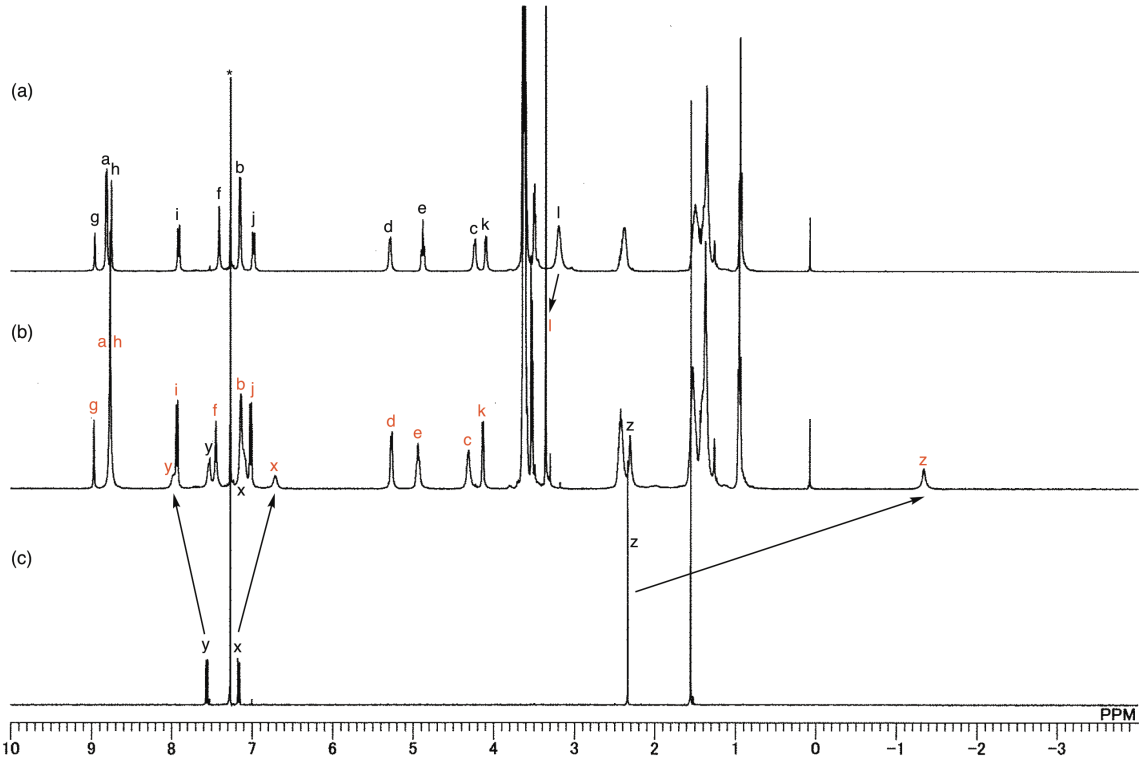


Fig. S17 Association behavior of self-assembled capsule $\mathbf{1}_2$•(*trans*-**2b**)$_4$ (2 mM) with guest **G1**, monitored by ^{1}H NMR ($CDCl_3$, 298 K): (a) $\mathbf{1}_2$•(*trans*-**2b**)$_4$ alone, (b) $\mathbf{1}_2$•(*trans*-**2b**)$_4$ + **G1** (2 equiv), and (c) **G1** alone. The marked signals are assigned in Scheme 2a. The representative signals of free **G1** and guest-free $\mathbf{1}_2$•(*trans*-**2b**)$_4$ are shown in black, and the representative signals of **G1**@[$\mathbf{1}_2$•(*trans*-**2b**)$_4$] are shown in red. The asterisk is the residual solvent signal.

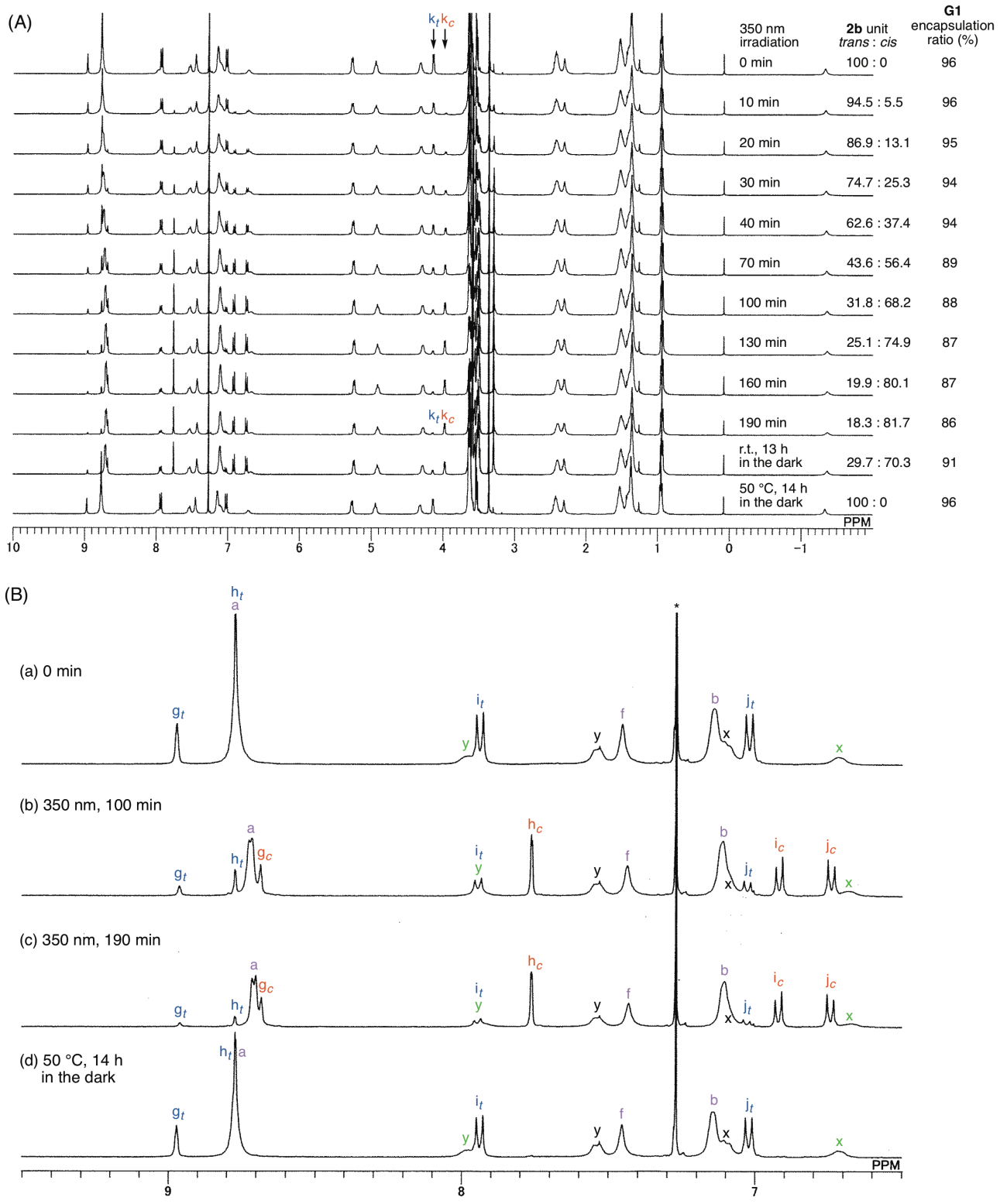


Fig. S18 ^{1}H NMR spectral changes ($CDCl_3$, 298 K) of **G1**@[$\mathbf{1}_2$•(*trans*-**2b**)$_4$] (initial state: [$\mathbf{1}_2$•(*trans*-**2b**)$_4$]$_{initial}$ = 2 mM and [**G1**]$_{initial}$ = 4 mM) upon 350 nm irradiation with a 300 W Xe lamp through a color filter for 350 nm light.
(A) Full spectra with *trans*:*cis* ratios of the subunit **2b** and **G1**-encapsulation ratios as a function of 350 nm irradiation time (min) and upon thermal reversion under light shielding.
(B) Selective spectra of Fig. S18A in the region between 9.5 and 6.5 ppm: (a) before irradiation, (b) after irradiation for 100 min, (c) after irradiation for 190 min, and (d) after heating at 50 °C for 14 h under light shielding. The signals marked a–*l* and x–z are assigned in Scheme 2a. The representative signals of the subunit **1** are shown in purple, and the representative signals of free and encapsulated **G1** are shown in black and green, respectively. The representative signals of the subunits *trans*-**2b** and *cis*-**2b** are shown in blue and red, respectively. The subscript '*t*' and '*c*' indicate the subunits *trans*-**2b** and *cis*-**2b**, respectively. Asterisk is the residual solvent signal.