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Enhanced reactivity of twisted amides inside a molecular cage

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1. Materials and instrumentations

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III NMR spectrometer, an AVANCE 500 NMR spectrometer (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR) and a JEOL ECA600 NMR spectrometer (600 MHz for ^1H NMR and 151 MHz for ^{13}C NMR) at 300 K unless otherwise stated. TMS (CDCl_3 solution) in a capillary served as an internal standard ($\delta = 0$ ppm for ^1H and ^{13}C NMR). Single crystal X-ray diffraction data were collected on a BRUKER APEX-II CCD rotating anode diffractometer equipped with focusing mirrors with MoK_α ($\lambda = 0.71073 \text{ \AA}$) radiation under cryogenic conditions, which are controlled with a cryostat system equipped with a N_2 generator (Japan Thermal Eng. Co., Ltd.). IR measurements were carried out using a DIGILAB Scimitar FTS-2000 instrument. GC-MS spectra were obtained on an Agilent 5977B Mass Selective Detector equipped with a 7820A GC system and an EI source. Solvents and reagents were purchased from TCI Co., Ltd., WAKO Pure Chemical Industries Ltd., and Sigma-Aldrich Co. Deuterated H_2O was acquired from Cambridge Isotope Laboratories, Inc. and used as supplied for the complexation reactions and NMR measurements. Coordination cages **1a**,¹ **1b**² and amide **2e**³ were prepared according to the reported methods.

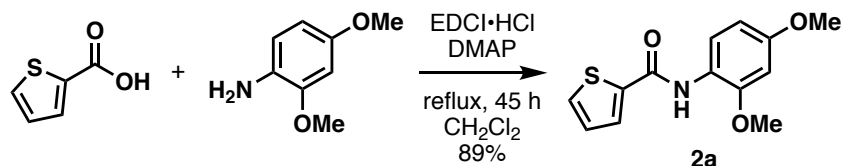
2. Syntheses of amides 2

Synthesis of *N*-(2,4-dimethoxyphenyl)-4-methoxybenzamide (**2a**)

p-Anisic acid (304 mg, 2.00 mmol), 2,4-dimethoxyaniline (306 mg, 2.00 mmol) and 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (503 mg, 2.03 mmol) were dissolved in tetrahydrofuran (15 mL) and stirred at room temperature for 12 h. The resulted mixture was concentrated *in vacuo*, diluted with 20 mL of ethyl acetate, and washed with HCl aq. (1 M, 10 mL), sat. NaHCO₃ aq. (10 mL), water (10 mL) and brine (10 mL). The organic layer was then dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by recrystallization from ethyl acetate to provide *N*-(2,4-dimethoxyphenyl)-4-methoxybenzamide (**2a**)⁴ as a white crystalline solid (547 mg, 1.90 mmol, 95%).

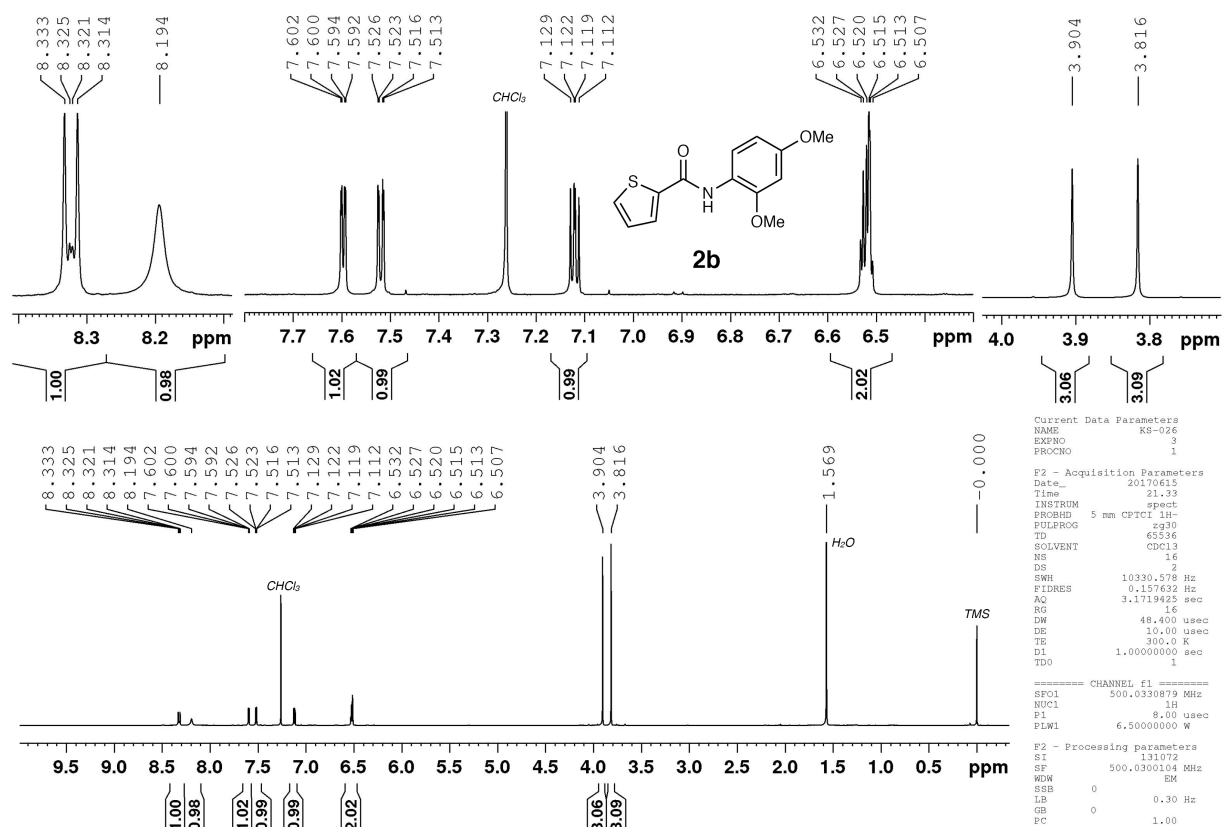
Physical data of 2a: ¹H NMR (500 MHz, 300 K, CDCl₃) : δ 3.82 (s, 3H, -OMe), 3.88 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 6.51–6.54 (m, 2H, ArH), 6.98 (d, *J* = 9.0 Hz, 2H, ArH), 7.85 (d, *J* = 8.5 Hz, 2H, ArH), 8.39 (d, *J* = 9.0 Hz, 1H, ArH); GC-MS (EI): *m/z* = 287.1 [M]⁺

Synthesis of *N*-(2,4-dimethoxyphenyl)thiophene-2-carboxamide (**2b**)

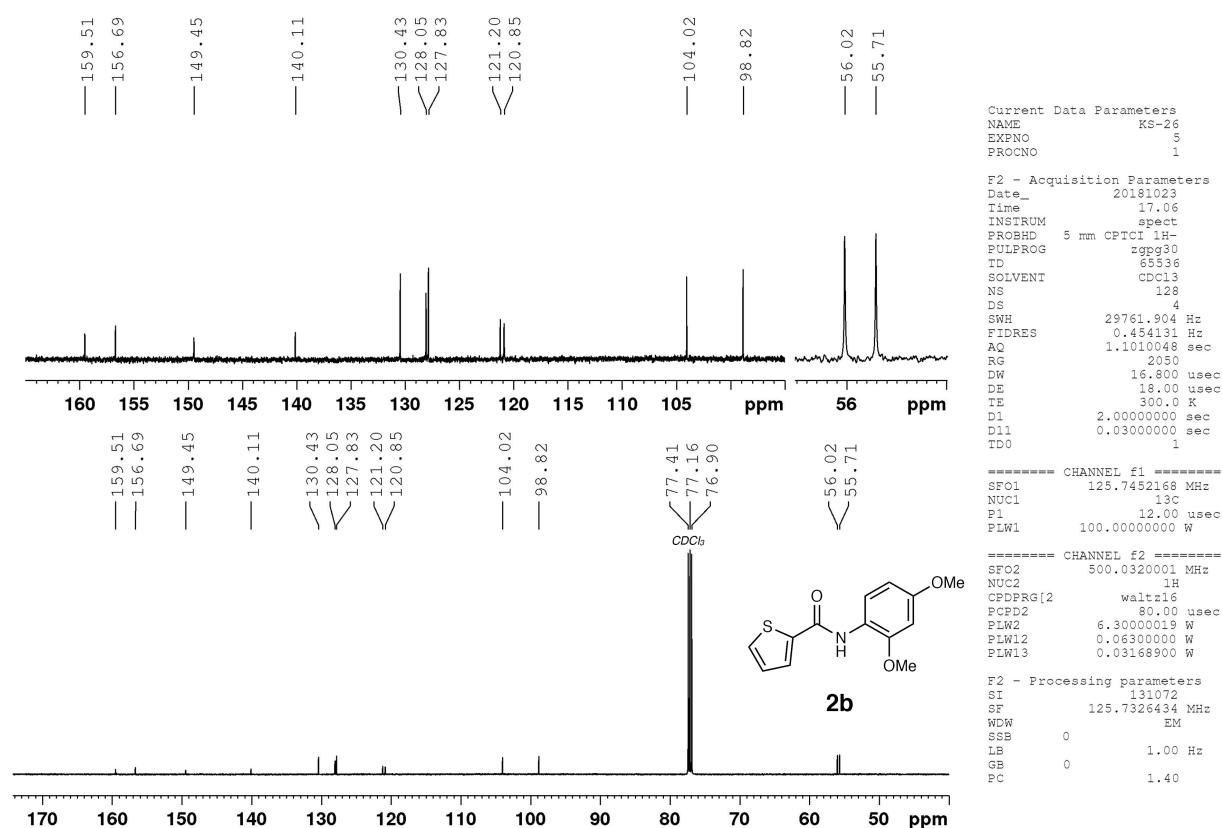


2-Thiophenecarboxylic acid (639 mg, 5.00 mmol), 2,4-dimethoxyaniline (764 mg, 4.99 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.15 g, 6.00 mmol) and 4-dimethylaminopyridine (729 mg, 5.97 mmol) were dissolved in dichloromethane (50 mL) and stirred at reflux conditions for 45 h. The reaction mixture was washed with HCl aq. (1 M, 10 mL), sat. NaHCO₃ aq. (10 mL) and brine and concentrated *in vacuo*. The crude product was purified by washing with Et₂O to provide *N*-(2,4-dimethoxyphenyl)thiophene-2-carboxamide (**2b**) as a white solid (1.17 g, 4.45 mmol, 89%).

Physical data of 2b: ¹H NMR (500 MHz, 300 K, CDCl₃) : δ 3.82 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 6.50–6.53 (m, 2H, ArH), 7.12 (dd, *J* = 3.5, 5.0 Hz, 1H, ArH), 7.52 (dd, *J* = 1.5, 5.0 Hz, 1H, ArH), 7.60 (dd, *J* = 1.0, 4.0 Hz, 1H, ArH), 8.20 (s, 1H, -NH-), 8.32 (dd, *J* = 4.0, 6.0 Hz, 1H, ArH); ¹³C NMR (125 MHz, CDCl₃, 300 K): δ 55.7 (CH₃), 56.0 (CH₃), 98.8 (CH), 104.0 (CH), 120.9 (CH), 121.2 (C), 127.8 (CH), 128.1 (CH), 130.4 (CH), 140.1 (C), 149.5 (C), 156.7 (C), 159.5 (C); IR (ATR, cm⁻¹): 3227, 1636, 1592, 1538, 1507, 1421, 1309, 1306, 1271, 1207, 1154, 1132, 1028, 928, 885, 859, 822, 798, 741, 715, 688, 649, 630, 592, 518; GC-MS(EI) calcd for C₁₃H₁₃NO₃S⁺ ([M]⁺) 263.1, found 263.1.; elemental analysis (calcd., found for C₁₃H₁₃NO₃S): C (59.30, 59.36), H (4.98, 5.02), N (5.32, 5.30); m.p.: 143–144 °C.



Supplementary Figure 1. ¹H NMR (500 MHz, 300 K, CDCl₃) spectrum of 2b.



Supplementary Figure 2. ¹³C NMR (125 MHz, 300 K, CDCl₃) spectrum of 2b.

Synthesis of *N*-(2,4-dimethoxyphenyl)furan-2-carboxamide (**2c**)

2-Furancarboxylic acid (560 mg, 5.00 mmol) was used instead of 2-thiophenecarboxylic acid in the synthesis of **2c**. *N*-(2,4-dimethoxyphenyl)furan-2-carboxamide was obtained as a white solid (861 mg, 3.48 mmol, 70%). Identification of the product was conducted by comparison of ¹H NMR and GC–MS spectra with literature data.⁵

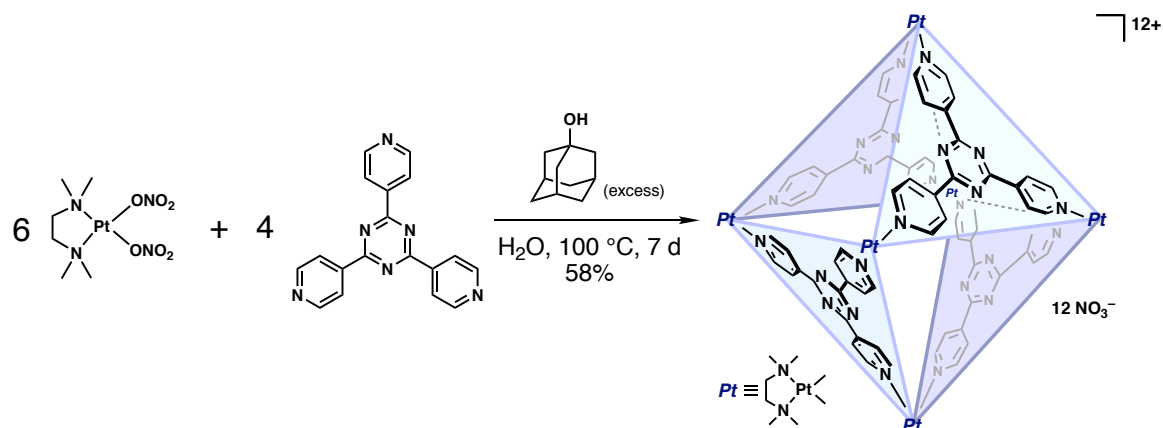
Physical data of 2c: ¹H NMR (500 MHz, 300 K, CDCl₃) : δ 3.82 (s, 3H, -OMe), 3.92 (s, 3H, -OMe), 6.50–6.53 (m, 2H, ArH), 6.54 (dd, *J* = 1.5, 3.5 Hz, 1H, ArH), 7.19 (dd, *J* = 0.5, 3.5 Hz, 1H, ArH), 7.51 (dd, *J* = 1.0, 1.5 Hz, 1H, ArH), 8.36 (dd, *J* = 2.5, 6.5 Hz, 1H, ArH), 8.56 (s, 1H, -NH-); ¹³C NMR (125 MHz, CDCl₃, 300 K): δ 55.6 (CH₃), 55.9 (CH₃), 98.8 (CH), 103.9 (CH), 112.5 (CH), 114.6 (CH), 120.7 (CH), 120.9 (C), 144.1 (CH), 148.4 (C), 149.5 (C), 155.8 (C), 156.6 (C); GC-MS(EI) calcd for C₁₃H₁₃NO₄⁺ ([M]⁺) 247.1, found 247.1.

Synthesis of *N*-(2,4-dimethoxyphenyl)-2-methoxybenzamide (**2d**)

o-Anisic acid (760 mg, 5.00 mmol), 2,4-dimethoxyaniline (769 mg, 5.02 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.17 g, 6.10 mmol) and 4-dimethylaminopyridine (730 mg, 5.98 mmol) were dissolved in dichloromethane (50 mL) and stirred at reflux conditions for 3 d. The reaction mixture was washed with HCl aq. (1 M, 10 mL), sat. NaHCO₃ aq. (10 mL) and brine and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate = 3:1→1:1→0:1) to provide *N*-(2,4-dimethoxyphenyl)-2-methoxybenzamide (**2d**) as a white solid (1.26 g, 4.37 mmol, 87%). Identification of the product was conducted by comparison of ¹H NMR and GC–MS spectra with literature data.⁶

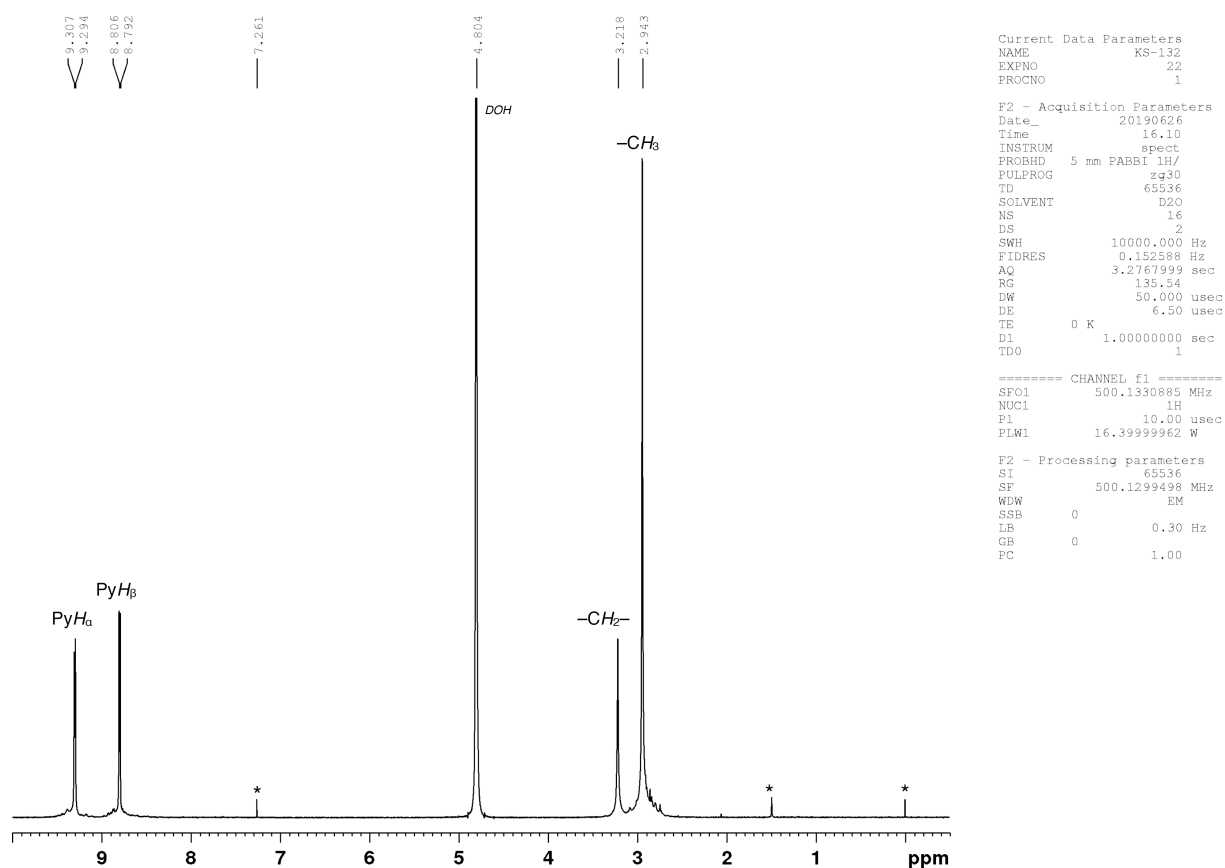
Physical data of 2d: ¹H NMR (500 MHz, 300 K, CDCl₃) : δ 3.82 (s, 3H, -OMe), 3.93 (s, 3H, -OMe), 4.06 (s, 3H, -OMe), 6.52–6.54 (m, 2H, ArH), 7.02 (d, *J* = 8.5 Hz, 2H, ArH), 7.11–7.14 (t, *J* = 7.5 Hz, 1H, ArH), 7.46–7.49 (dt, *J* = 2.0, 8.0 Hz, 1H, ArH), 8.30 (dd, *J* = 2.0, 8.0 Hz, 1H, ArH), 8.53 (dd, *J* = 9.5 Hz, 1H, ArH), 10.41 (s, 1H, -NH-); ¹³C NMR (125 MHz, CDCl₃, 300 K): δ 55.7 (CH₃), 56.17 (CH₃), 56.21 (CH₃), 99.0 (CH), 104.3 (CH), 111.8 (CH), 121.3 (CH), 121.7 (CH), 122.6 (C), 122.7 (C), 132.5 (CH), 132.9 (CH), 149.8 (C), 156.4 (C), 157.5 (C), 162.7 (C); GC-MS(EI): calcd for C₁₆H₁₇NO₄⁺ ([M]⁺) 287.1, found 287.1.

Synthesis of cage 1c

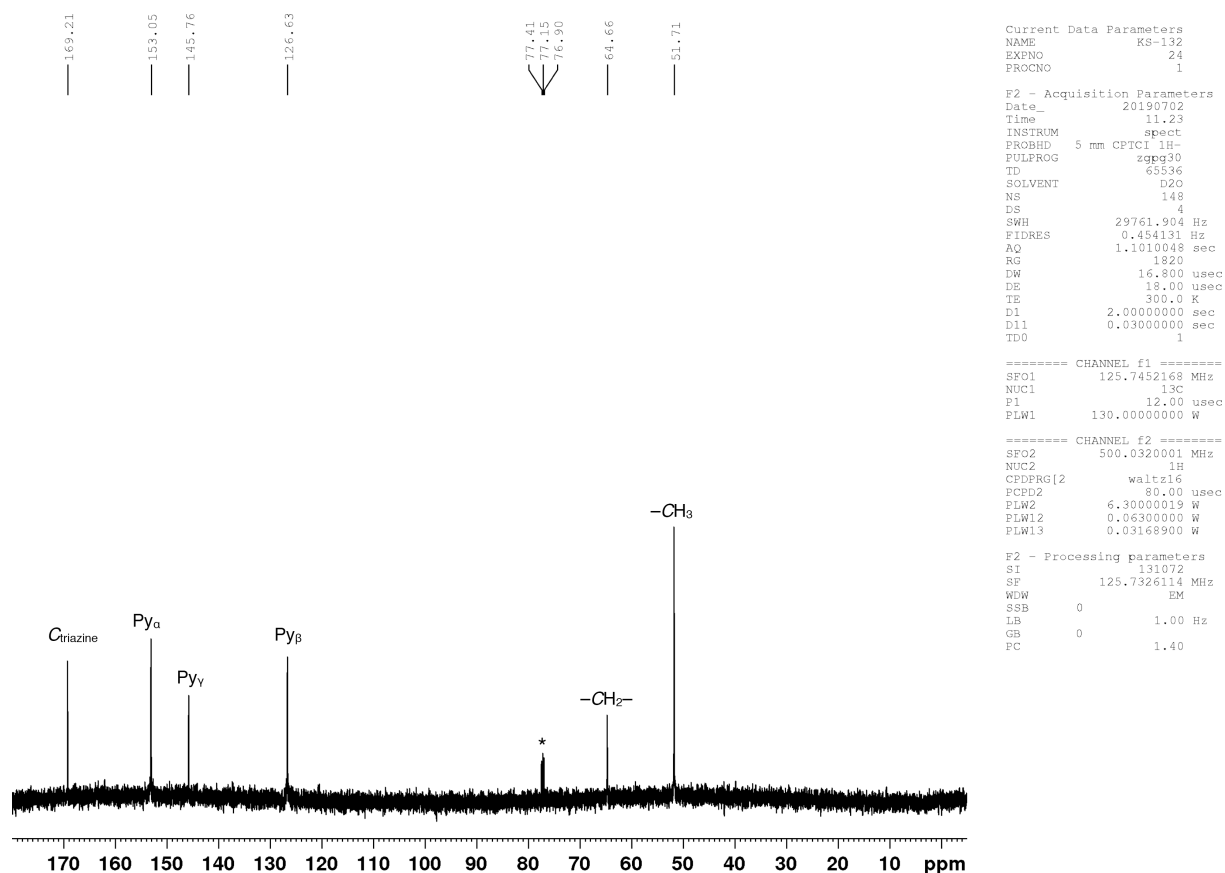


2,4,6-Tris(4-pyridyl)-1,3,5-triazine (703 mg, 2.25 mmol) and 1-adamantyltoluene (856 mg, 5.63 mmol) were suspended in an aqueous solution (30 mL) of *cis*-(*N,N,N',N'*-tetramethylethylenediamine) dinitratoplatinum (II) (1.47 g, 3.38 mmol) and the mixture was stirred at $100\text{ }^\circ\text{C}$ for 7 d. The solution was filtered and concentrated *in vacuo*. The crude solid was recrystallized from hot water. The crystalline powder was dissolved in water and washed with chloroform. The resulted aqueous solution was freeze-dried to give self-assembled coordination cage **1c** as white powder (1.27 g, 0.329 mmol, 58%).

Physical data of 1c: ^1H NMR (500 MHz, D_2O , 300 K): δ 2.94 (s, 72H, CH_3), 3.22 (s, 24H, CH_2), 8.80 (d, $J = 6.5$ Hz, 24H, PyH_β), 9.30 (d, $J = 6.5$ Hz, 24H, PyH_α); ^{13}C NMR (125 MHz, D_2O , 300 K): δ 51.71 (CH_3), 64.66 (CH_2), 126.63 (Py_β), 145.76 (Py_γ); 153.05 (Py_α), 169.21 (triazine), IR (ATR, cm^{-1}): 3418, 1636, 1526, 1374, 1332, 1316, 815; m.p.: $> 250\text{ }^\circ\text{C}$ (decomposed); elemental analysis (calcd., found for $\text{C}_{108}\text{H}_{144}\text{N}_{48}\text{O}_{36}\text{Pt}_6 \cdot 21\text{H}_2\text{O}$): C (30.60, 30.58), H (4.42, 4.53), N (15.86, 15.77).



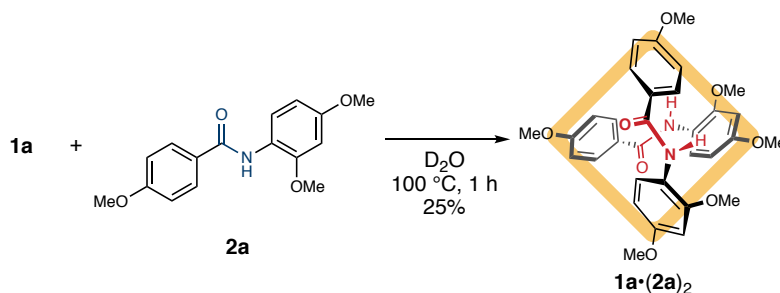
Supplementary Figure 3. ^1H NMR (500 MHz, 300 K, D_2O) spectrum of **1c**. Asterisks denotes peaks from the internal standard.



Supplementary Figure 4. ^{13}C NMR (125 MHz, 300 K, D_2O) spectrum of **1c**. Asterisk denotes peaks from the internal standard.

3. Inclusion of amides 2 into cage 1

Formation of inclusion complex $1a \cdot (2a)_2$: a typical procedure

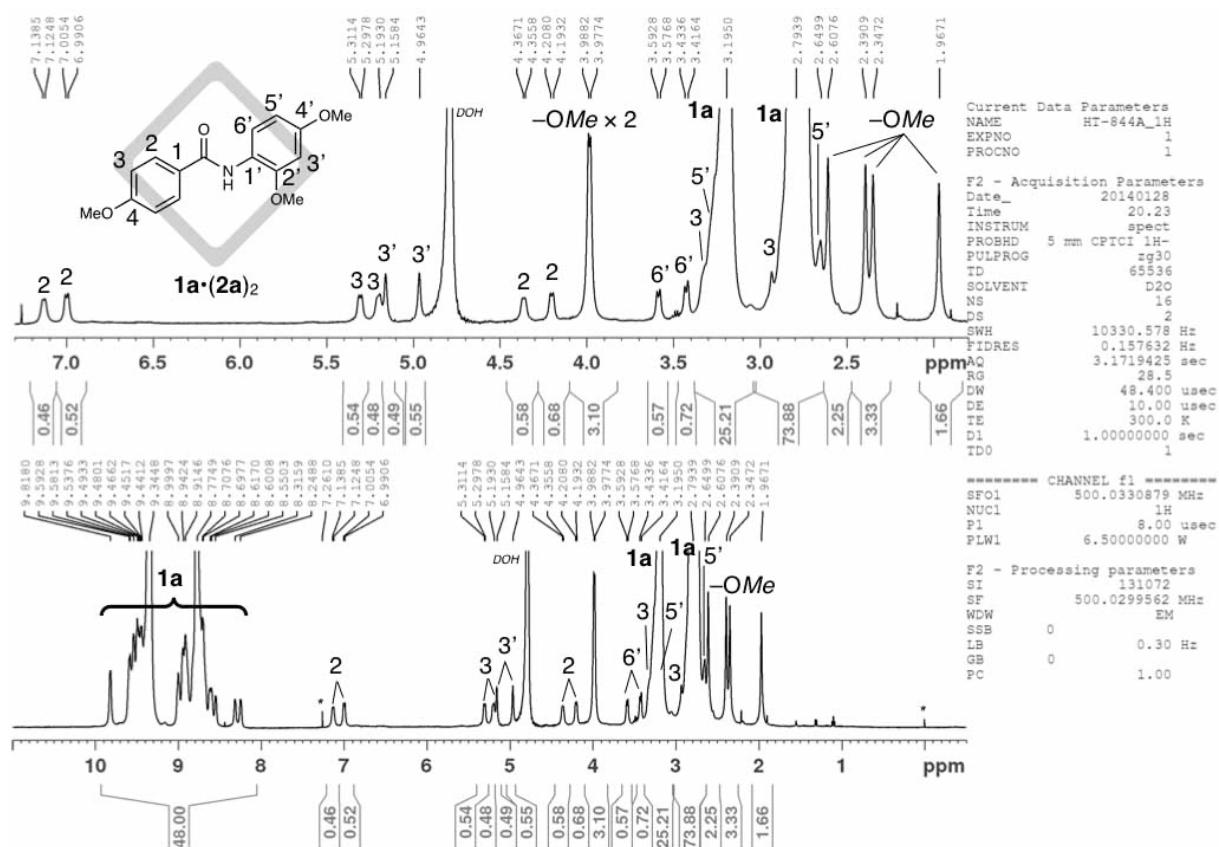


Amide **2a** (29.3 mg, 102 μ mol) was suspended in an aqueous solution of cage **1a** (20.0 mM, 1.0 mL) and stirred at 100 $^\circ$ C for 1 h. After removal of residual solid by filtration, the formation of inclusion complex $1a \cdot (2a)_2$ was confirmed by 1H NMR spectroscopy. The yield of $1a \cdot (2a)_2$ was determined as 25% from the integral ratio between **1a** and **2a**.

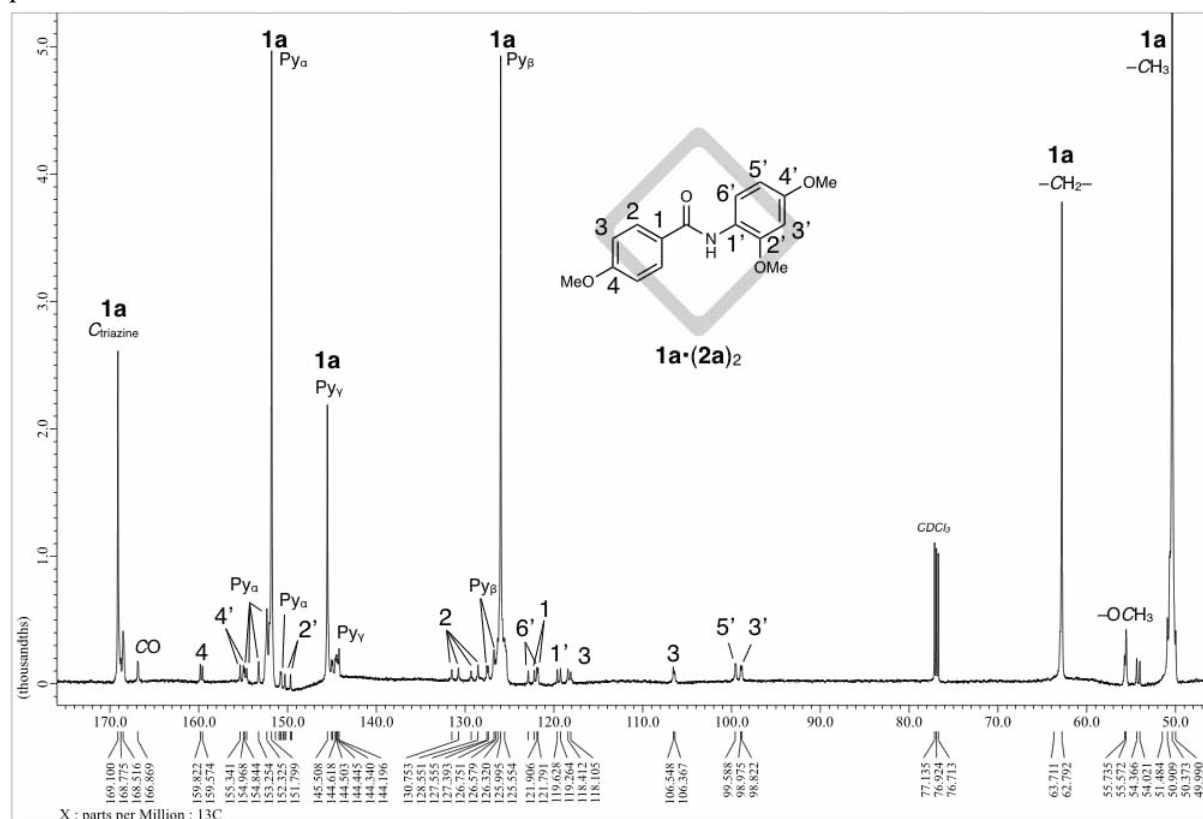


Physical data of $1a \cdot (2a)_2$: 1H NMR (500 MHz, D_2O , 300 K): δ 1.97 (s, 3H, **2a**, $-OMe$), 2.35 (s, 3H, **2a**, $-OMe$), 2.39 (s, 3H, **2a**, $-OMe$), 2.61 (s, 3H, **2a**, $-OMe$), 2.65 (br, 1H, **2a**, H-5'), 2.79 (72 H, **1a**, CH_3 , 1H, **2a**, H-3), 3.20 (24 H, **1a**, CH_2), 3.26 (1H, **2a**, H-5'), 3.36 (1H, **2a**, H-3), 3.42 (d, $J = 8.5$ Hz, 1H, **2a**, H-6'), 3.58 (d, $J = 8.5$ Hz, 1H, **2a**, H-6'), 3.98 (s, 3H, **2a**, $-OMe$), 3.99 (s, 3H, **2a**, $-OMe$), 4.20 (d, $J = 7$ Hz, 1H, **2a**, H-2), 4.36 (br, 1H, **2a**, H-2), 4.96 (s, 1H, **2a**, H-3'), 5.16 (s, 1H, **2a**, H-3'), 5.19

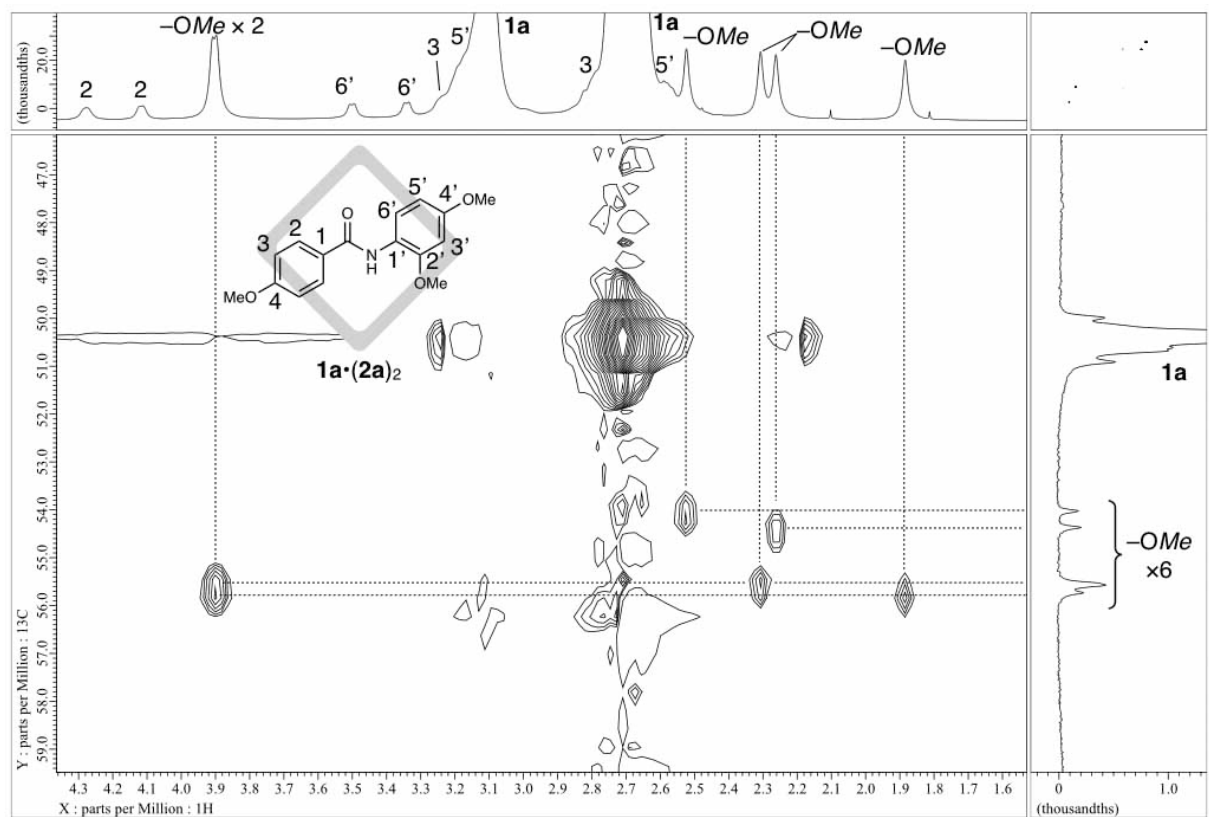
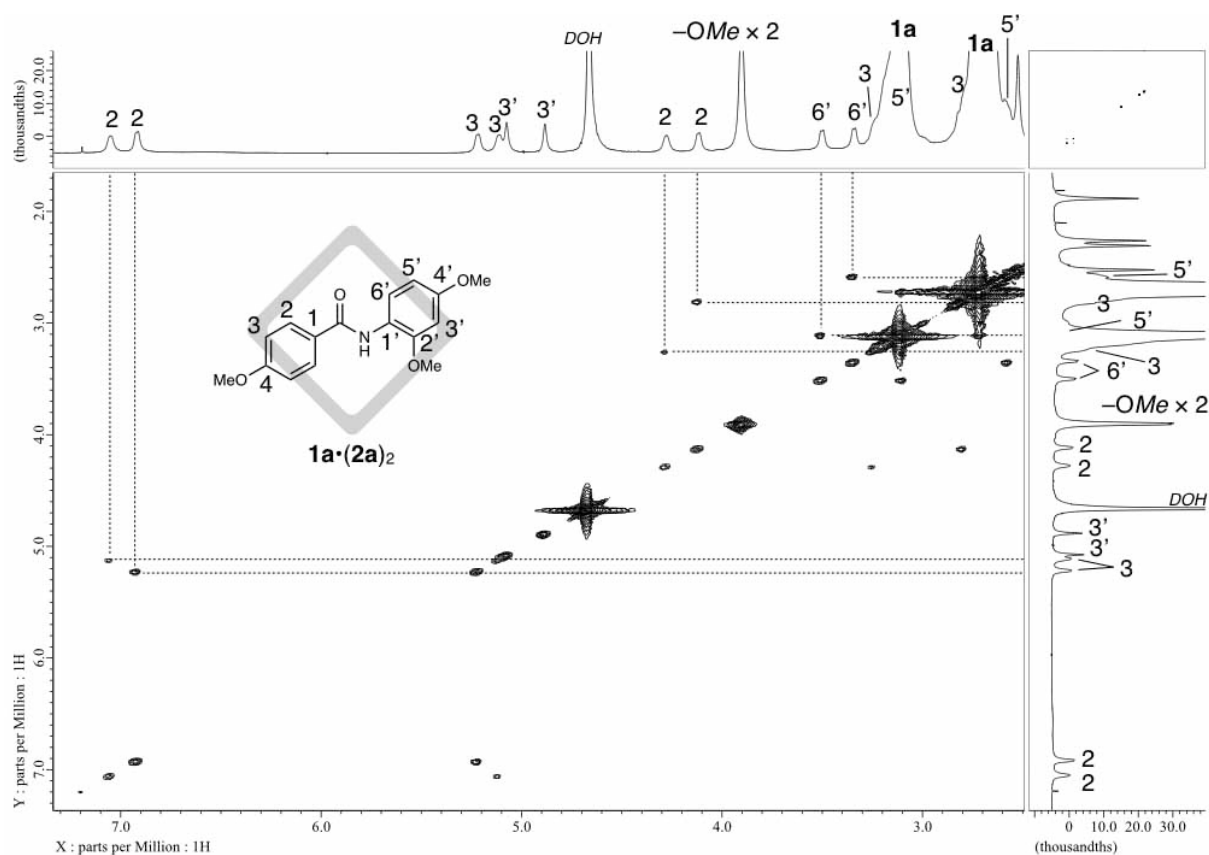
(br, 1H, **2a**, H-3), 5.30 (d, $J = 7$ Hz, 1H, **2a**, H-3), 7.00 (d, $J = 7$ Hz, 1H, **2a**, H-2), 7.13 (br, 1H, **2a**, H-2), 8.24–9.00 (24H, **1a**, PyH_β), 9.34–9.82 (24H, **1a**, PyH_α); ^{13}C NMR (151 MHz, D_2O , 300 K): δ 50.0 (**1a**, CH_3), 50.4 (**1a**, CH_3), 50.9 (**1a**, CH_3), 51.5 (**1a**, CH_3), 54.0 (**2a**, $-OMe$), 54.4 (**2a**, $-OMe$), 55.5 (**2a**, $-OMe$), 55.6 (**2a**, $-OMe \times 2$), 55.8 (**2a**, $-OMe$), 62.8 (**1a**, CH_2), 63.0 (**1a**, CH_2), 98.9 (**2a**, C-3'), 99.0 (**2a**, C-3'), 99.6 (**2a**, C-5'), 106.4 (**2a**, C-3), 106.5 (**2a**, C-3), 118.1 (**2a**, C-3), 118.4 (**2a**, C-3), 119.3 (**2a**, C-1'), 119.6 (**2a**, C-1'), 121.8 (**2a**, C-1), 121.9 (**2a**, C-6'), 122.2 (**2a**, C-1), 122.9 (**2a**, C-6'), 125.2–126.9 (**1a**, Py_β), 127.4 (**1a**, Py_β), 127.6 (**1a**, Py_β), 128.6 (**2a**, C-2), 129.3 (**2a**, C-2), 130.8 (**2a**, C-2), 131.5 (**2a**, C-2), 144.2 (**1a**, Py_γ), 144.3 (**1a**, Py_γ), 144.45 (**1a**, Py_γ), 144.50 (**1a**, Py_γ), 144.6 (**1a**, Py_γ), 144.9 (**1a**, Py_γ), 145.0 (**1a**, Py_γ), 145.5 (**1a**, Py_γ), 149.7 (**2a**, C-2'), 150.3 (**2a**, C-2'), 150.7 (**1a**, Py_α), 150.8 (**1a**, Py_α), 151.8 (**1a**, Py_α), 152.3 (**1a**, Py_α), 153.3 (**1a**, Py_α), 154.6 (**1a**, Py_α), 154.8 (**1a**, Py_α), 155.0 (**2a**, C-4'), 155.3 (**2a**, C-4'), 159.6 (**2a**, C-4), 159.8 (**2a**, C-4), 166.8 (**2a**, $-CONH-$), 166.9 (**2a**, $-CONH-$), 168.5 (**1a**, triazine), 169.1 (**1a**, triazine).

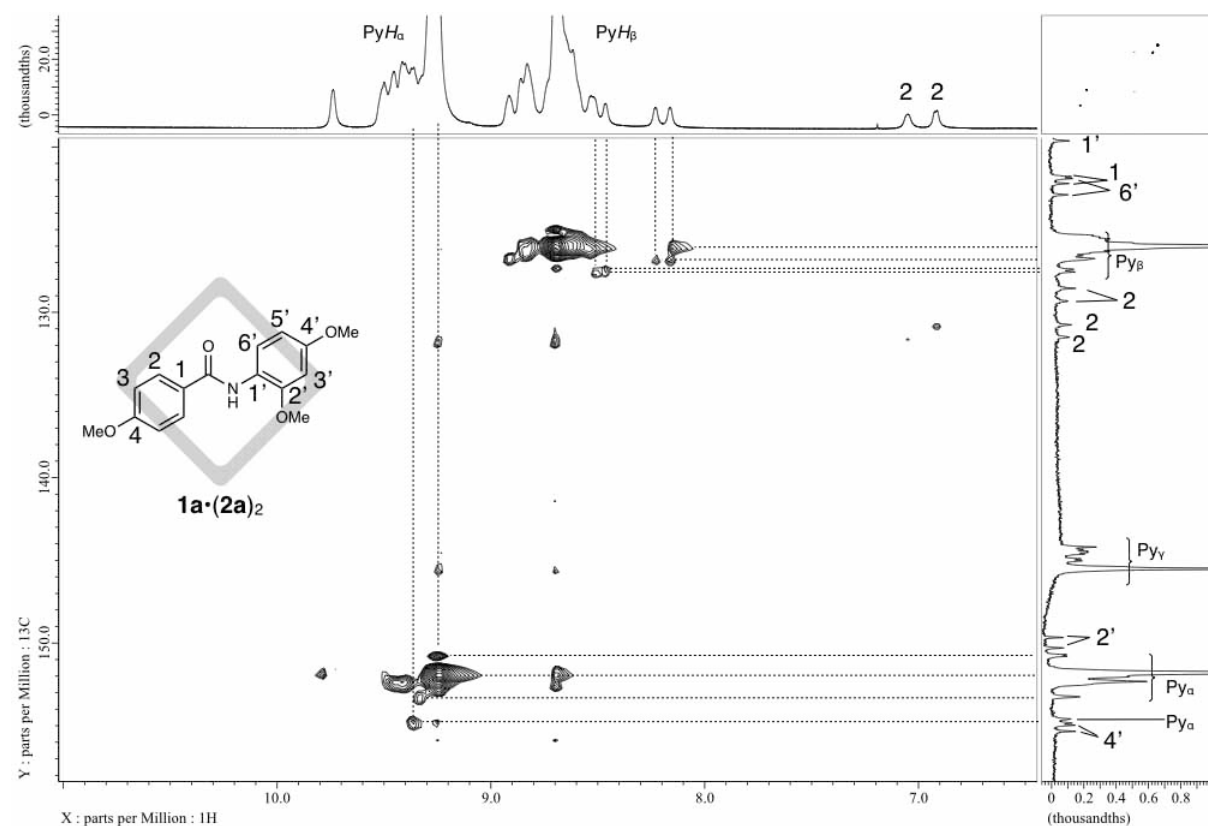
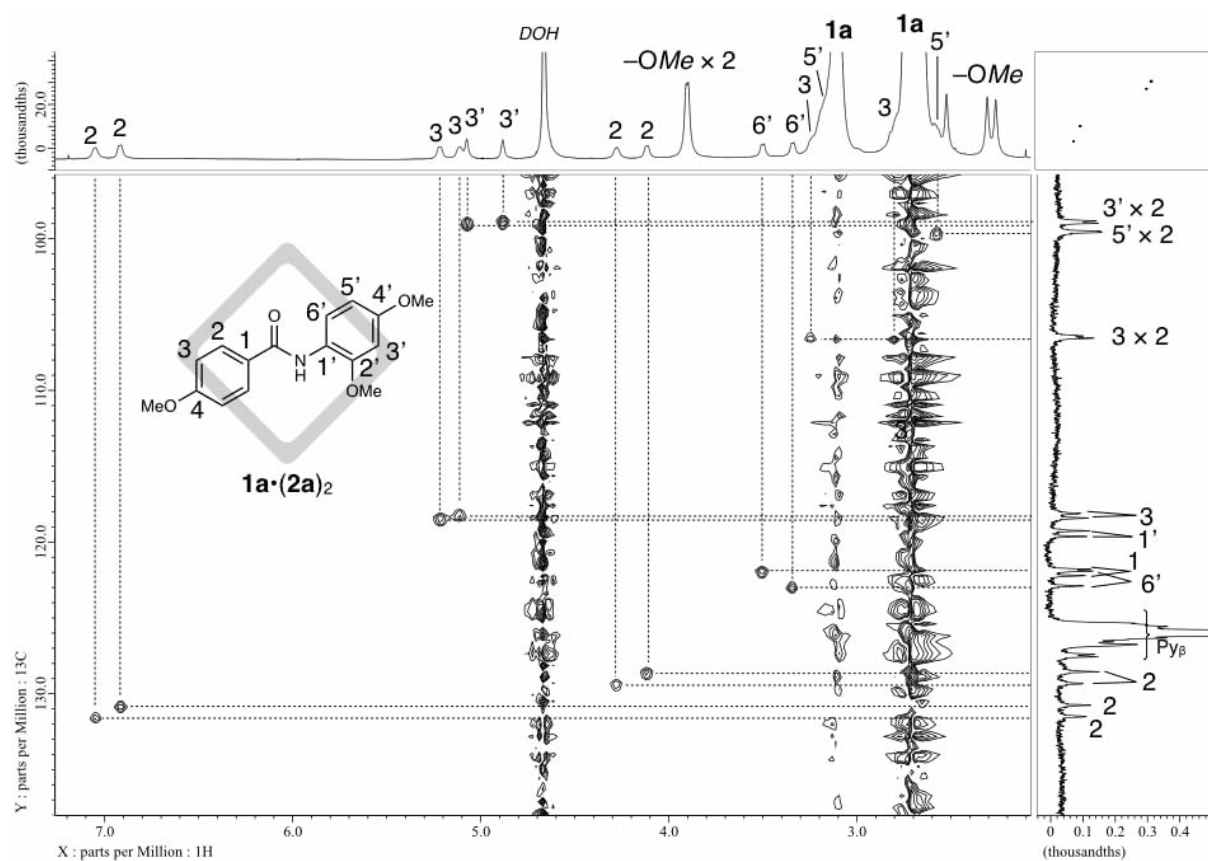


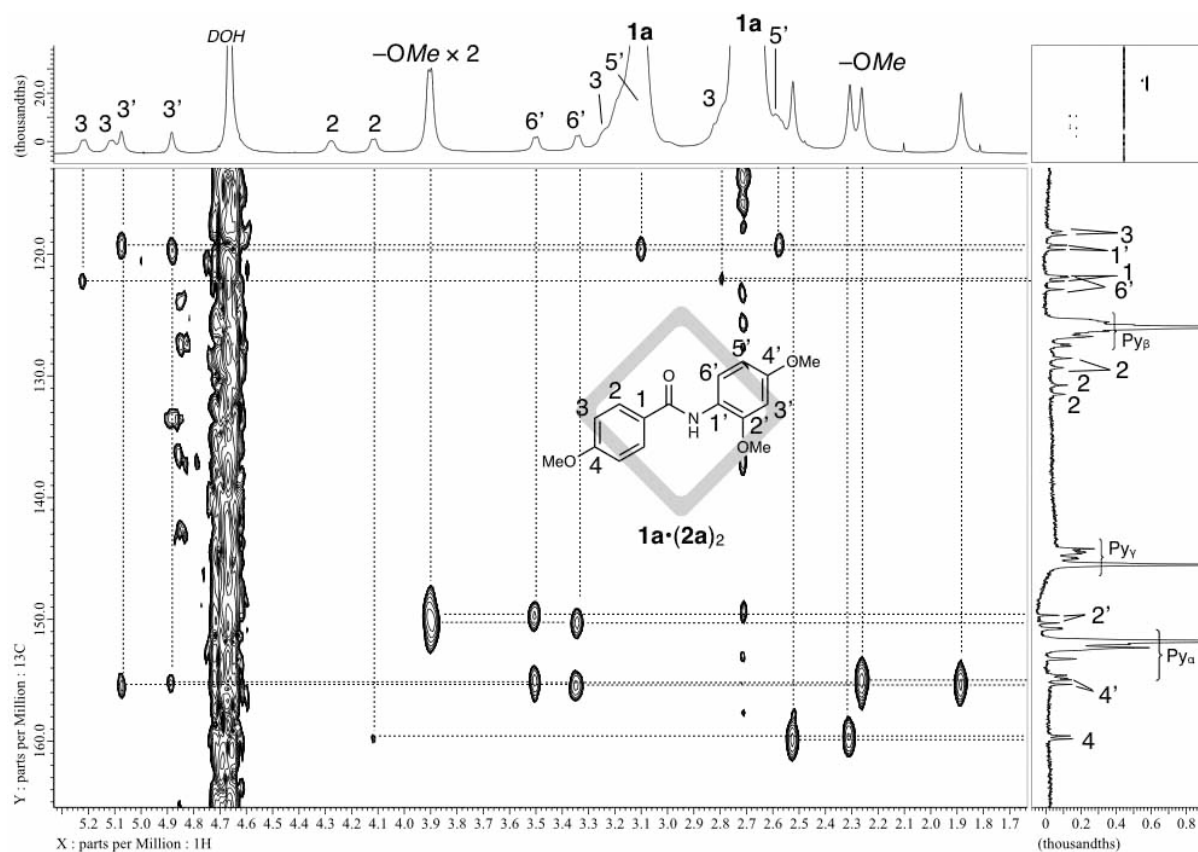
Supplementary Figure 5. ^1H NMR (500 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{a})_2$. Asterisks denotes peaks from the internal standard.



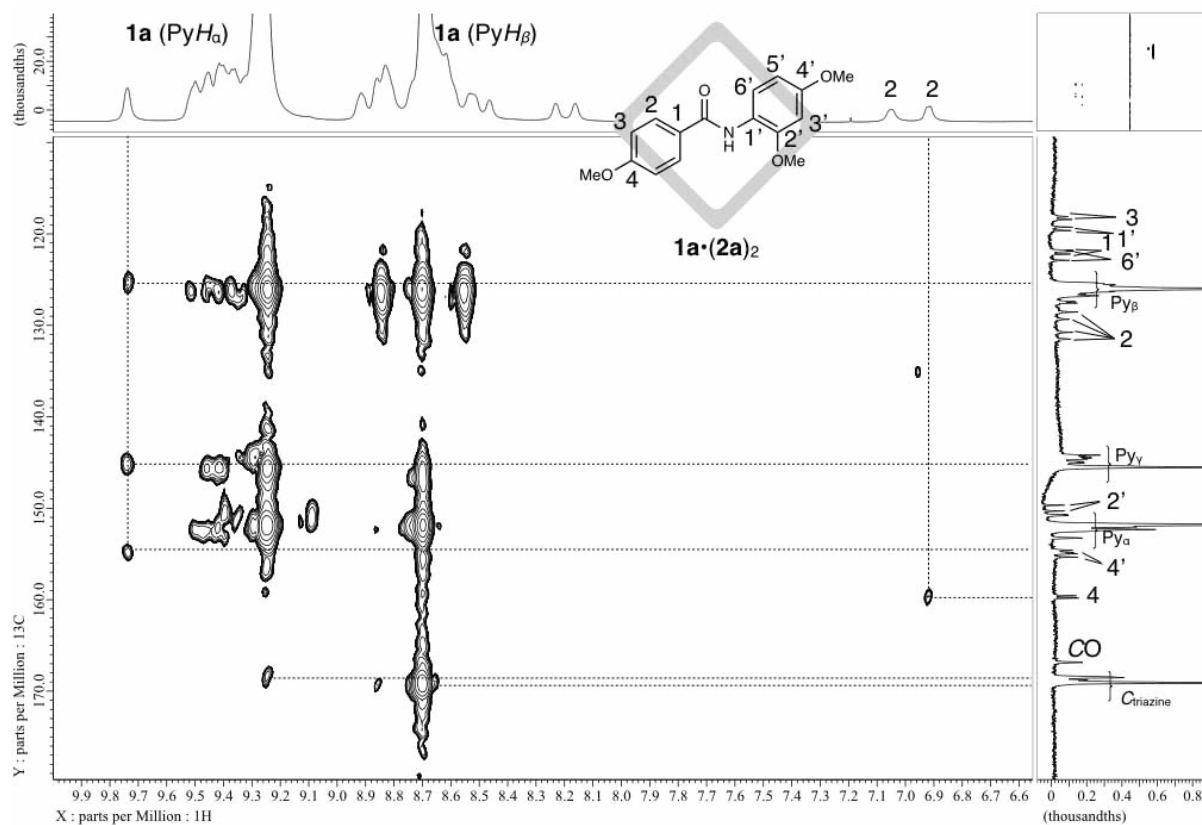
Supplementary Figure 6. ^{13}C NMR (151 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{a})_2$.





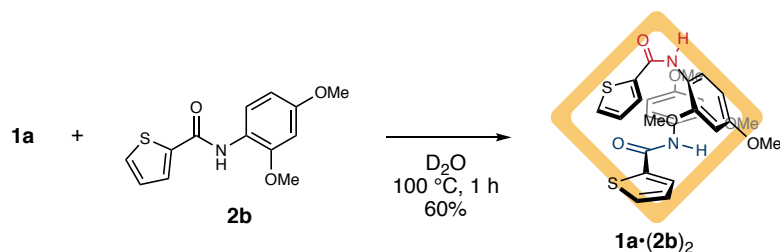


Supplementary Figure 11. ^1H - ^{13}C HMBC NMR (600 MHz, 300 K, D_2O) spectrum of $1\mathbf{a}\cdot(2\mathbf{a})_2$.



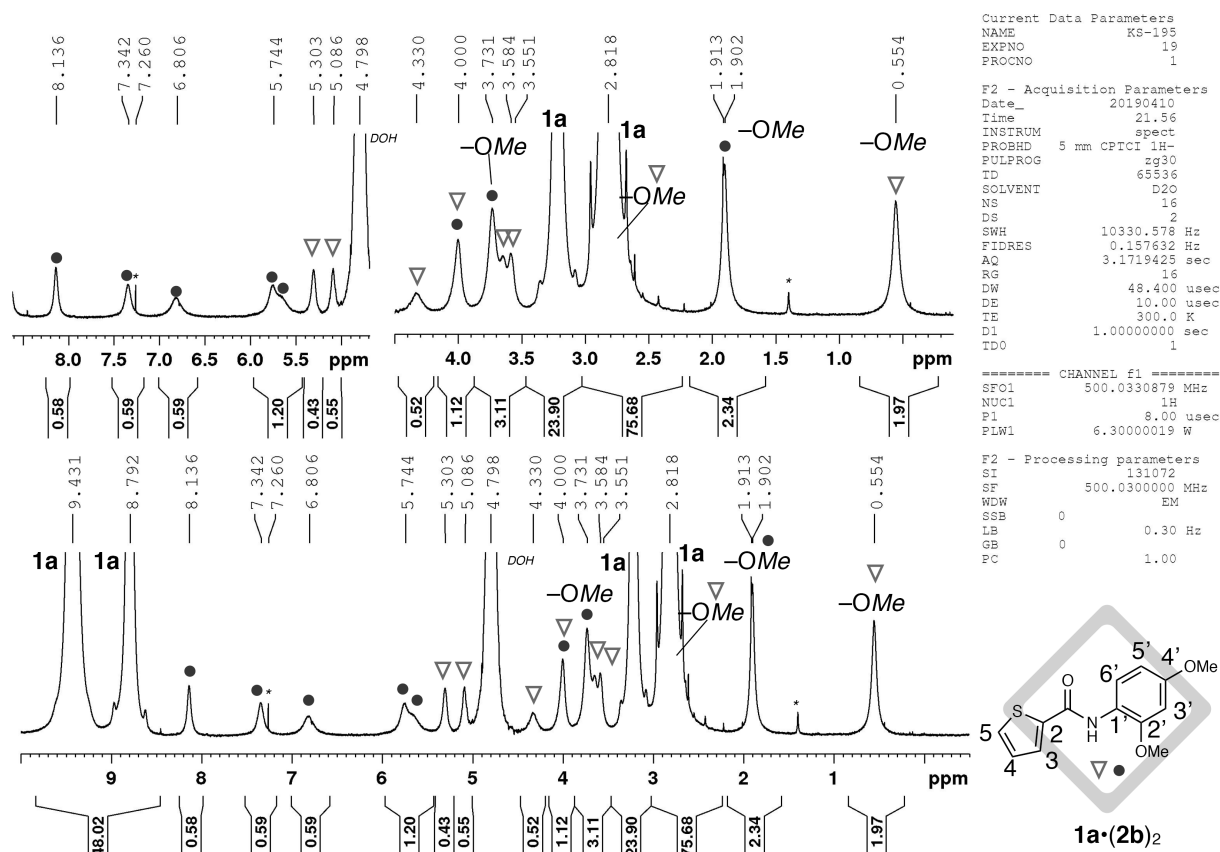
Supplementary Figure 12. ^1H - ^{13}C HMBC NMR (600 MHz, 300 K, D_2O) spectrum of $1\mathbf{a}\cdot(2\mathbf{a})_2$.

Formation of inclusion complex $1\bullet(2b)_2$

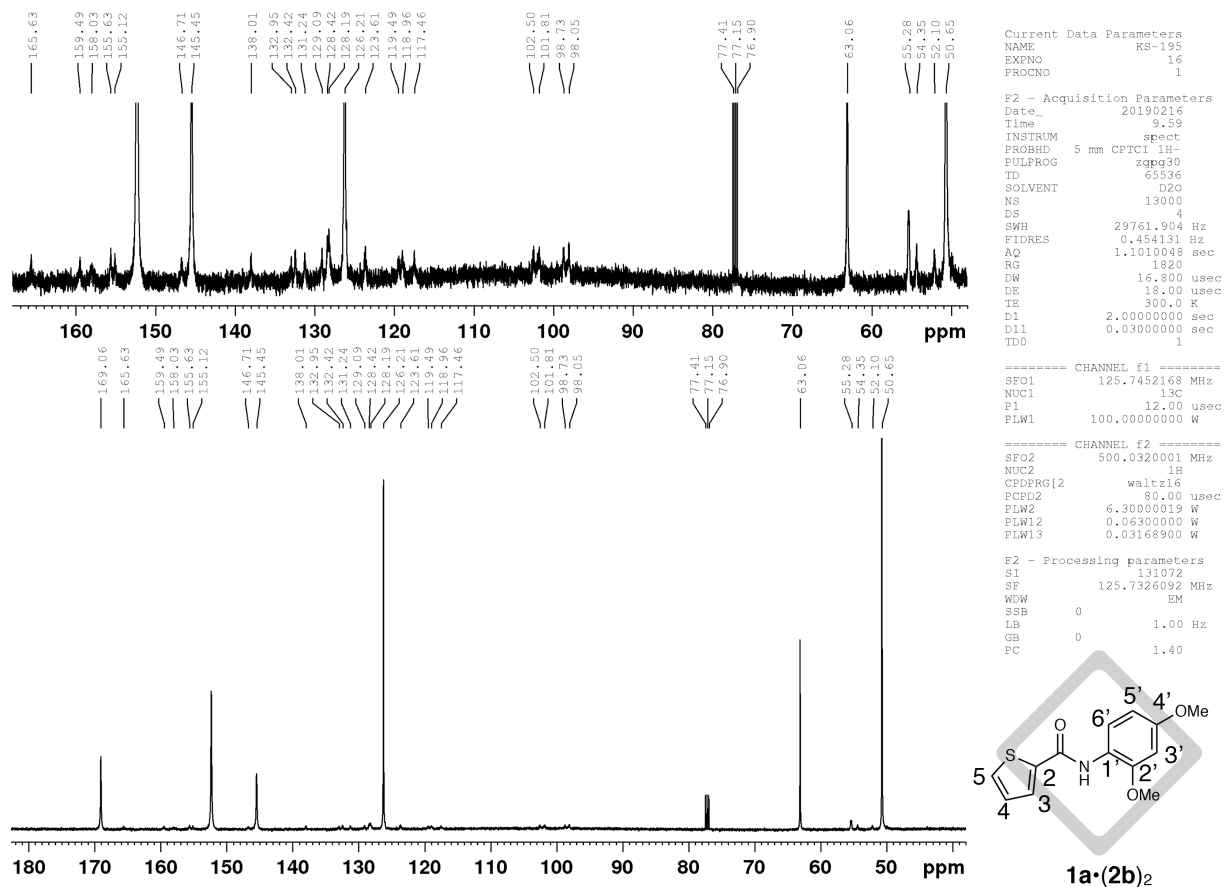


Inclusion complex $1a\bullet(2b)_2$ was formed from a mixture of **2b** (10.4 μmol , 5 eq.) and **1a** (20 mM, 1.0 mL) by stirring at 100 $^{\circ}\text{C}$ for 1 h (60% yield).

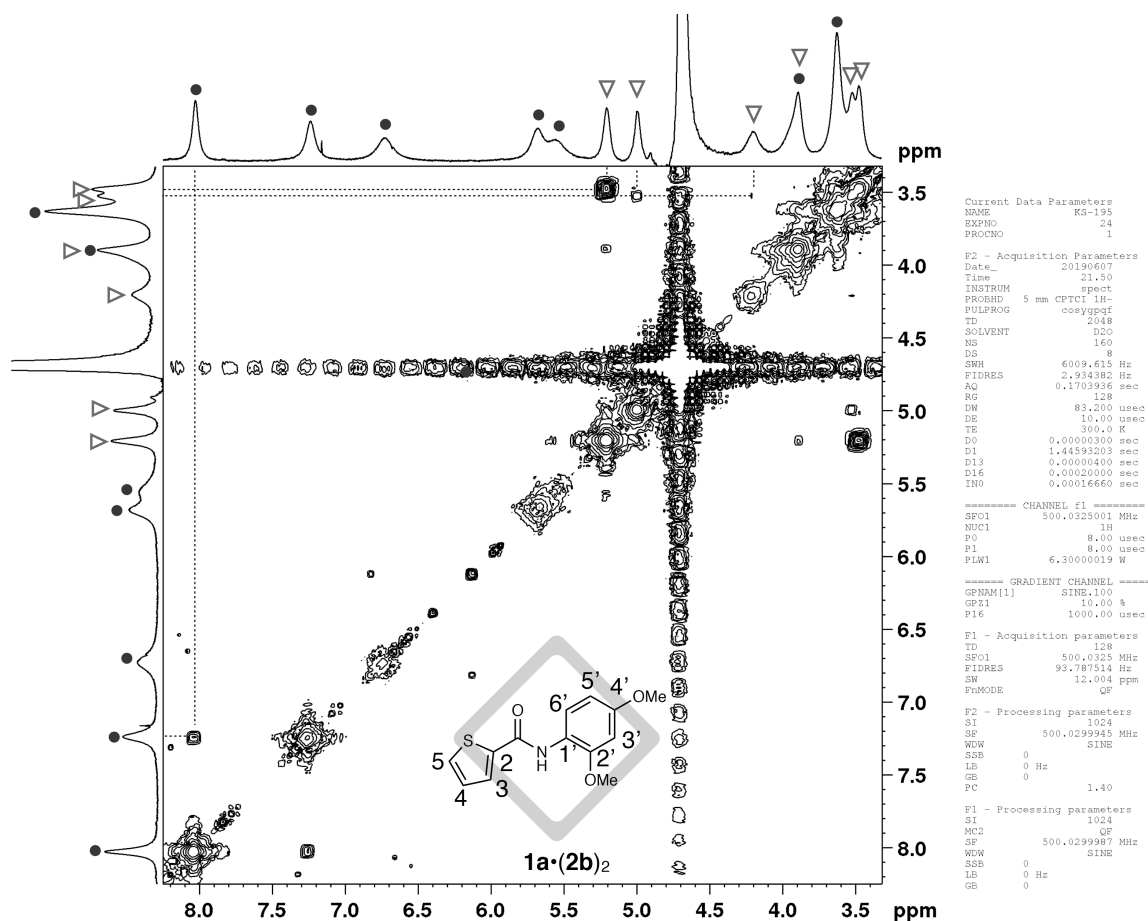
Physical data of $1a\bullet(2b)_2$: ^1H NMR (500 MHz, D_2O , 300 K): δ 0.55 (s, 3H, **2b**, $-\text{OMe}$), 1.90 (s, 3H, **2b**, $-\text{OMe}$), 2.82 (s, 72H, **1a**, CH_3 , 3H, **2b**, $-\text{OMe}$), 3.21 (s, 24H, **1a**, CH_2), 3.55 (br, 1H, **2b**, ArH), 3.58 (br, 1H, **2b**, ArH), 3.73 (br, 3H, **2b**, $-\text{OMe}$), 4.00 (br, 2H, **2b**, ArH $\times 2$), 4.33 (br, 1H, **2b**, ArH), 5.09 (br, 1H, **2b**, ArH), 5.30 (br, 1H, **2b**, ArH), 5.65 (br, 1H, **2b**, ArH), 5.74 (br, 1H, **2b**, ArH), 6.81 (br, 1H, **2b**, ArH), 7.34 (br, 1H, **2b**, ArH), 8.14 (br, 1H, **2b**, ArH), 8.79 (d, $J = 6.0$ Hz, 24H, **1a**, PyH $_{\beta}$), 9.43 (d, $J = 6.0$ Hz, 24H, **1a**, PyH $_{\alpha}$); ^{13}C NMR (125 MHz, D_2O , 300 K): δ 50.7 (**1a**, CH_3), 52.1 (**2b**, $-\text{OMe}$), 54.4 (**2b**, $-\text{OMe}$), 55.3 (**2b**, $-\text{OMe}\times 2$), 63.1 (**1a**, CH_2), 98.1 (**2b**, CH), 98.7 (**2b**, CH), 101.8 (**2b**, CH), 102.5 (**2b**, CH), 117.5 (**2b**, CH), 118.9 (**2b**, C), 119.5 (**2b**, C), 123.6 (**2b**, CH), 126.2 (**1a**, Py $_{\beta}$), 128.1 (**2b**, CH), 128.4 (**2b**, CH), 129.1 (**2b**, CH), 131.2 (**2b**, CH), 132.4 (**2b**, CH), 133.0 (**2b**, C), 138.0 (**2b**, C), 145.5 (**1a**, Py $_{\gamma}$), 146.7 (**2b**, C), 152.3 (**1a**, Py $_{\alpha}$), 155.1 (**2b**, C), 155.6 (**2b**, C), 158.0 (**2b**, C), 159.5 (**2b**, C), 165.6 (**2b**, C), 169.1 (**1a**, C $_{\text{triazine}}$).



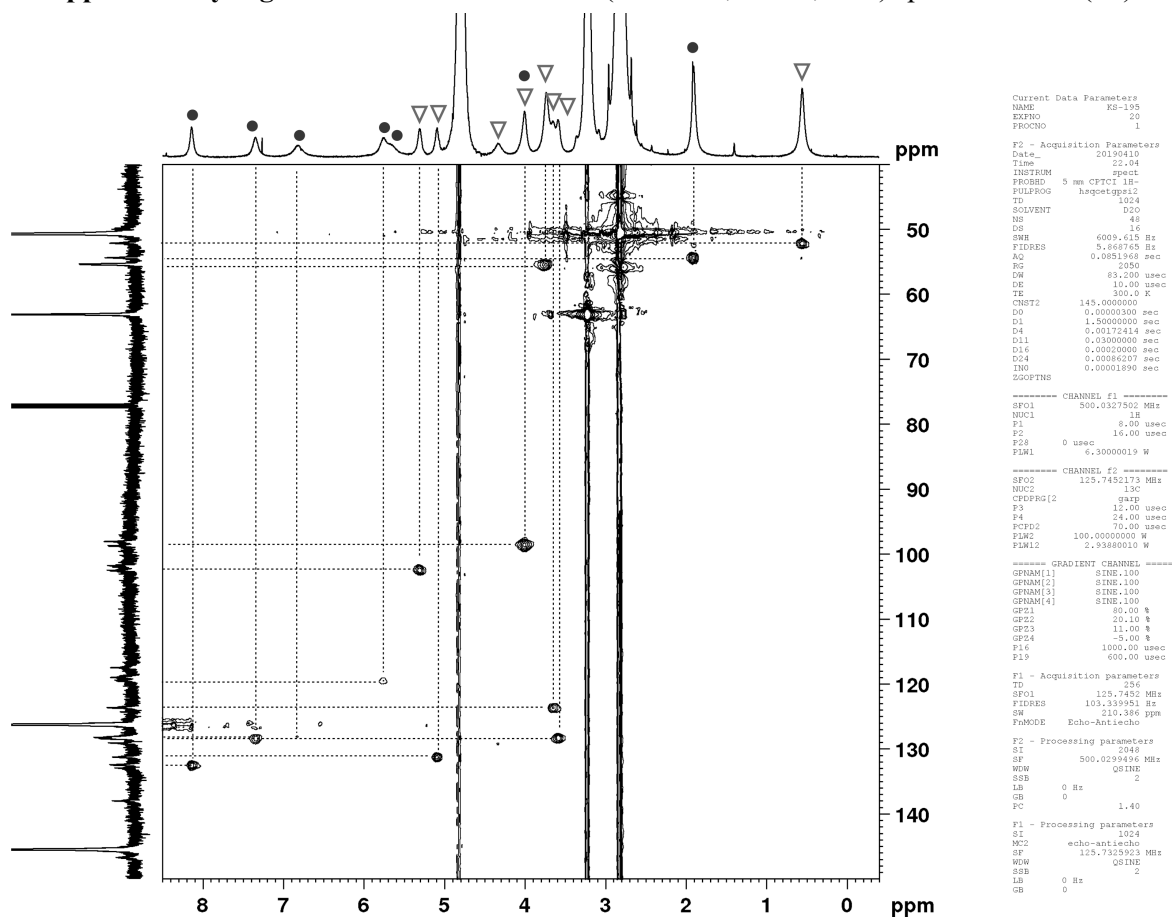
Supplementary Figure 13. ¹H NMR (500 MHz, 300 K, D₂O) spectrum of 1a•(2b)₂.



Supplementary Figure 14. ¹³C NMR (125 MHz, 300 K, D₂O) spectrum of 1a•(2b)₂.

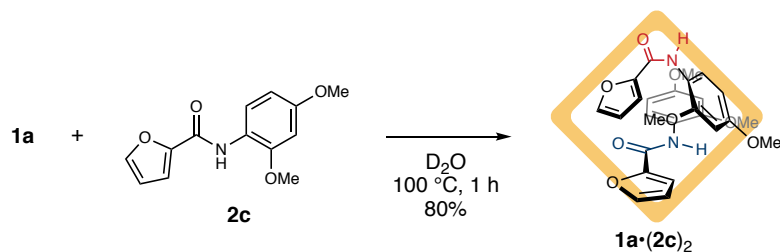


Supplementary Figure 15. ^1H - ^1H COSY NMR (500 MHz, 300 K, D_2O) spectrum of **1a•(2b)₂**.



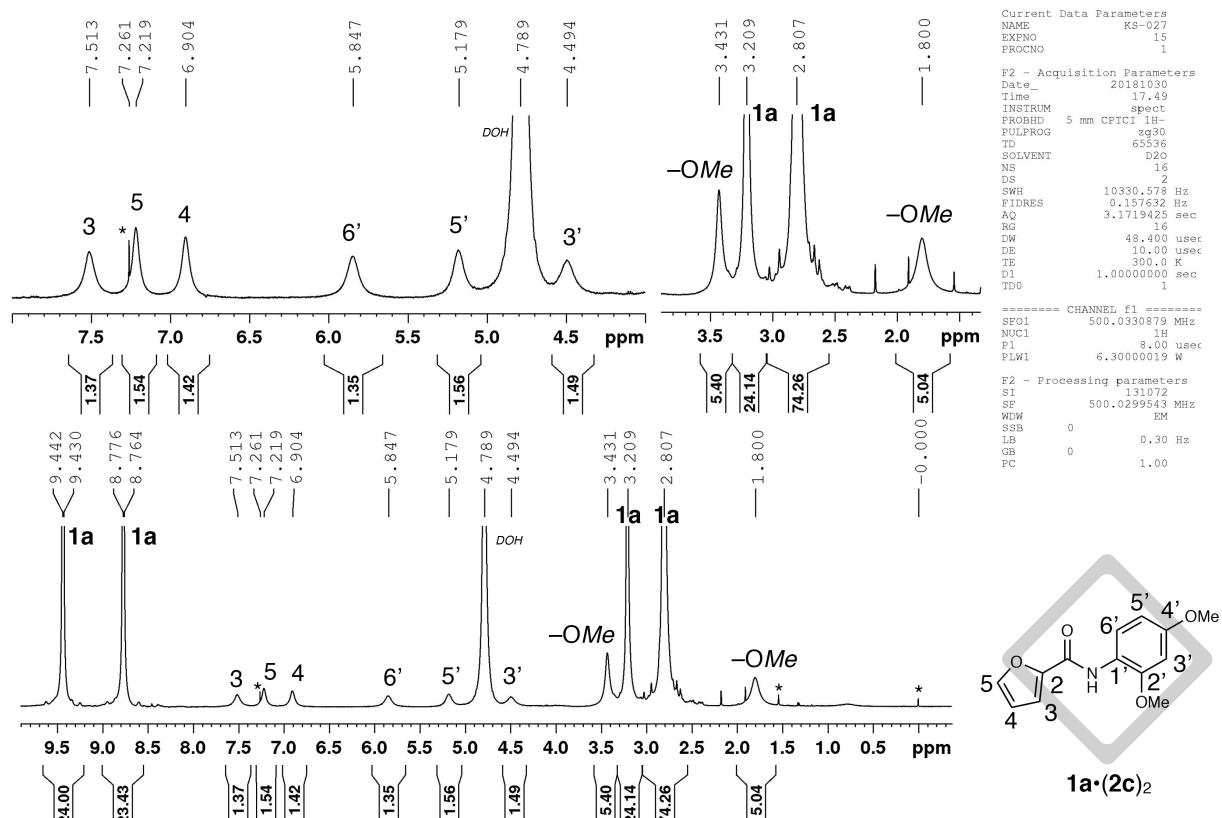
Supplementary Figure 16. ^1H - ^{13}C HSQC NMR (500 MHz, 300 K, D_2O) spectrum of **1a•(2b)₂**.

Formation of inclusion complex $1a \cdot (2c)_2$

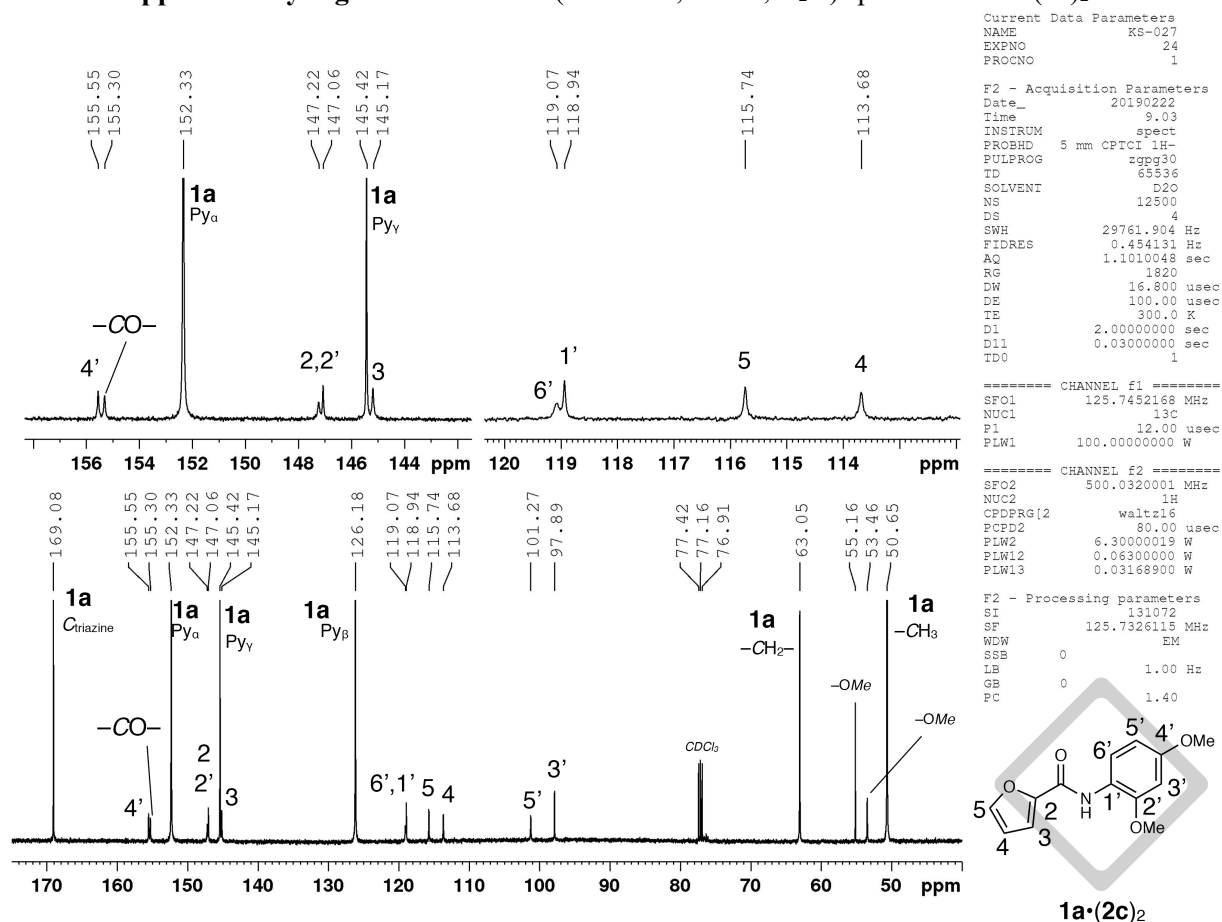


Inclusion complex $1a \cdot (2c)_2$ was formed from a mixture of **2c** (98.7 μ mol, 5 eq.) and **1a** (20 mM, 1.0 mL) by stirring at 100 $^\circ$ C for 1 h (80% yield).

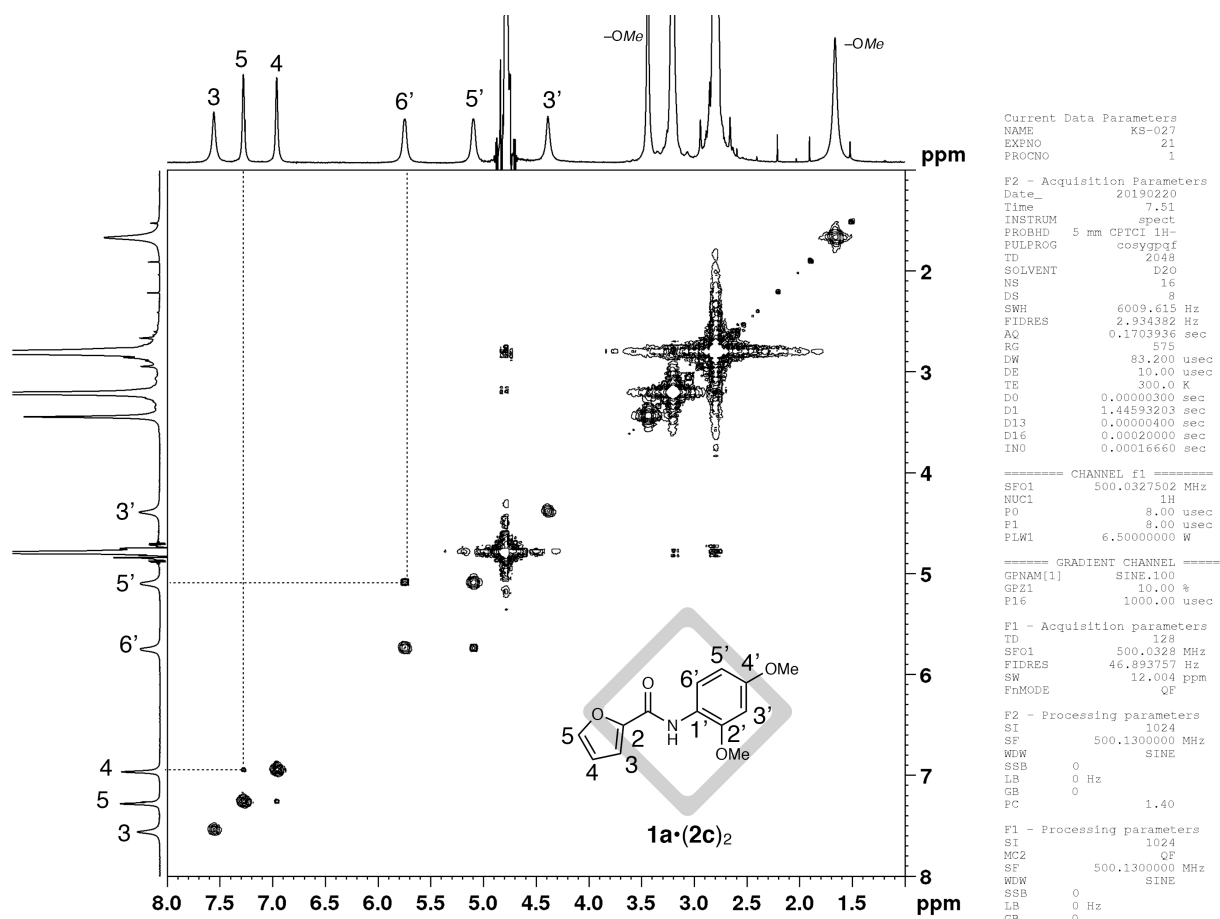
Physical data of $1a \cdot (2c)_2$: 1H NMR (500 MHz, D_2O , 300 K): δ 1.80 (s, 3H, **2c**, $-OMe$), 2.81 (s, 72H, **1a**, CH_3), 3.21 (s, 24H, **1a**, CH_2), 3.43 (s, 3H, **2c**, $-OMe$), 4.49 (br, 1H, **2c**, H-3'), 5.18 (br, 1H, **2c**, H-5'), 5.85 (br, 1H, **2c**, H-6'), 6.90 (br, 1H, **2c**, H-4), 7.21 (br, 1H, **2c**, H-5), 7.51 (br, 1H, **2c**, H-3), 8.77 (d, $J = 6.0$ Hz, 24H, **1a**, PyH_β), 9.44 (d, $J = 6.0$ Hz, 24H, **1a**, PyH_α); ^{13}C NMR (125 MHz, D_2O , 300 K): δ 50.7 (**1a**, CH_3), 53.5 (**2c**, $-OMe$), 55.2 (**2c**, $-OMe$), 63.1 (**1a**, CH_2), 97.9 (**2c**, C-3'), 101.3 (**2c**, C-5'), 113.7 (**2c**, C-4), 115.7 (**2c**, C-5), 118.9 (**2c**, C-1'), 119.1 (**2c**, C-6'), 126.2 (**1a**, Py_β), 145.2 (**2c**, C-3), 145.4 (**1a**, Py_γ), 147.1, 147.2 (**2c**, C-2, C-2'), 152.3 (**1a**, Py_α), 155.3 (**2c**, $-CONH-$), 155.6 (**2c**, C-4'), 169.1 (**1a**, $C_{triazine}$).



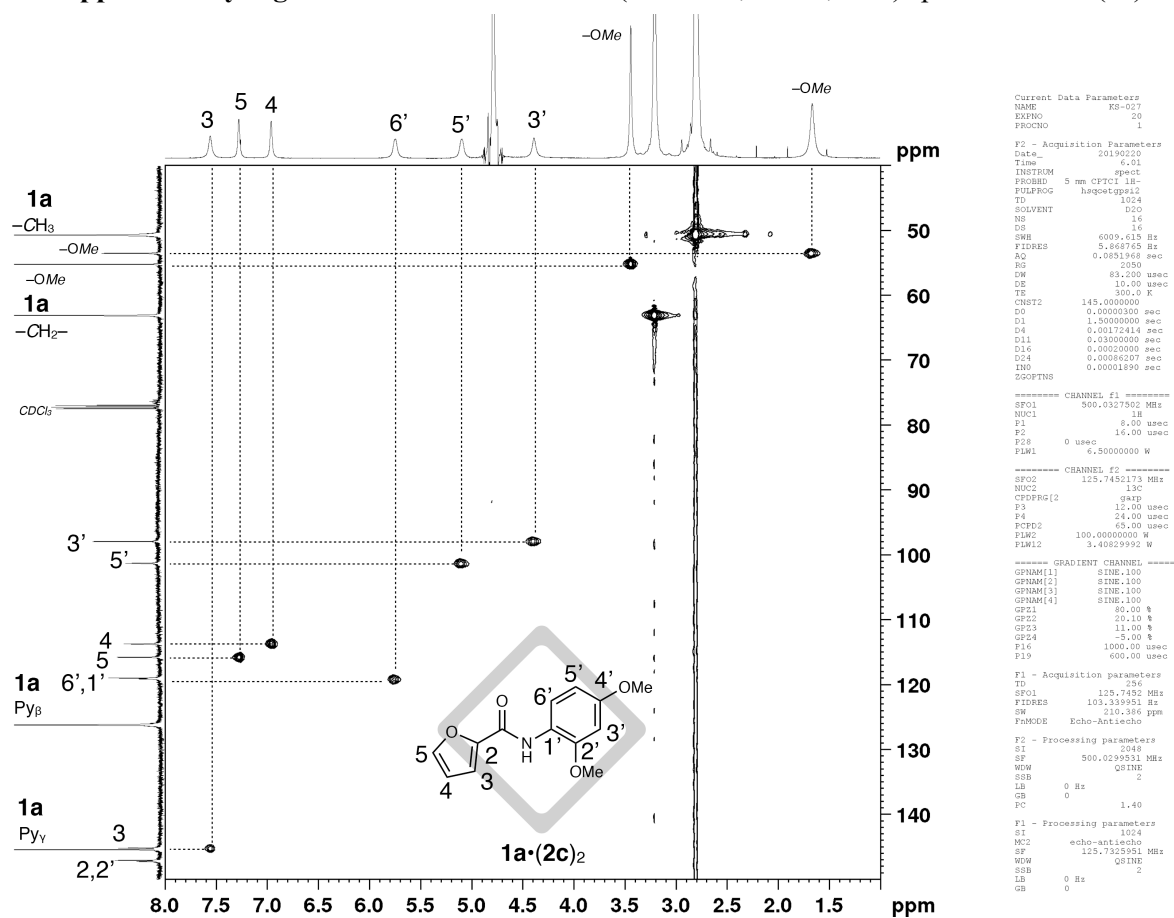
Supplementary Figure 17. ¹H NMR (500 MHz, 300 K, D₂O) spectrum of **1a•(2c)₂**.



Supplementary Figure 18. ¹³C NMR (125 MHz, 300 K, D₂O) spectrum of **1a•(2c)₂**.

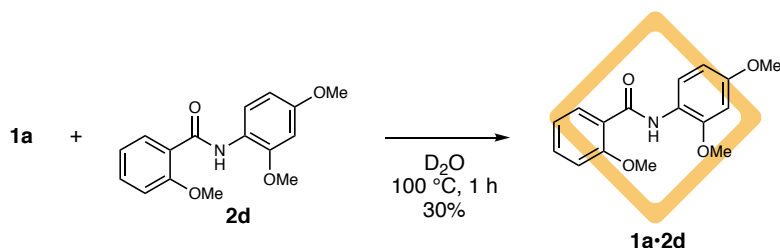


Supplementary Figure 19. ^1H - ^1H COSY NMR (500 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{c})_2$.



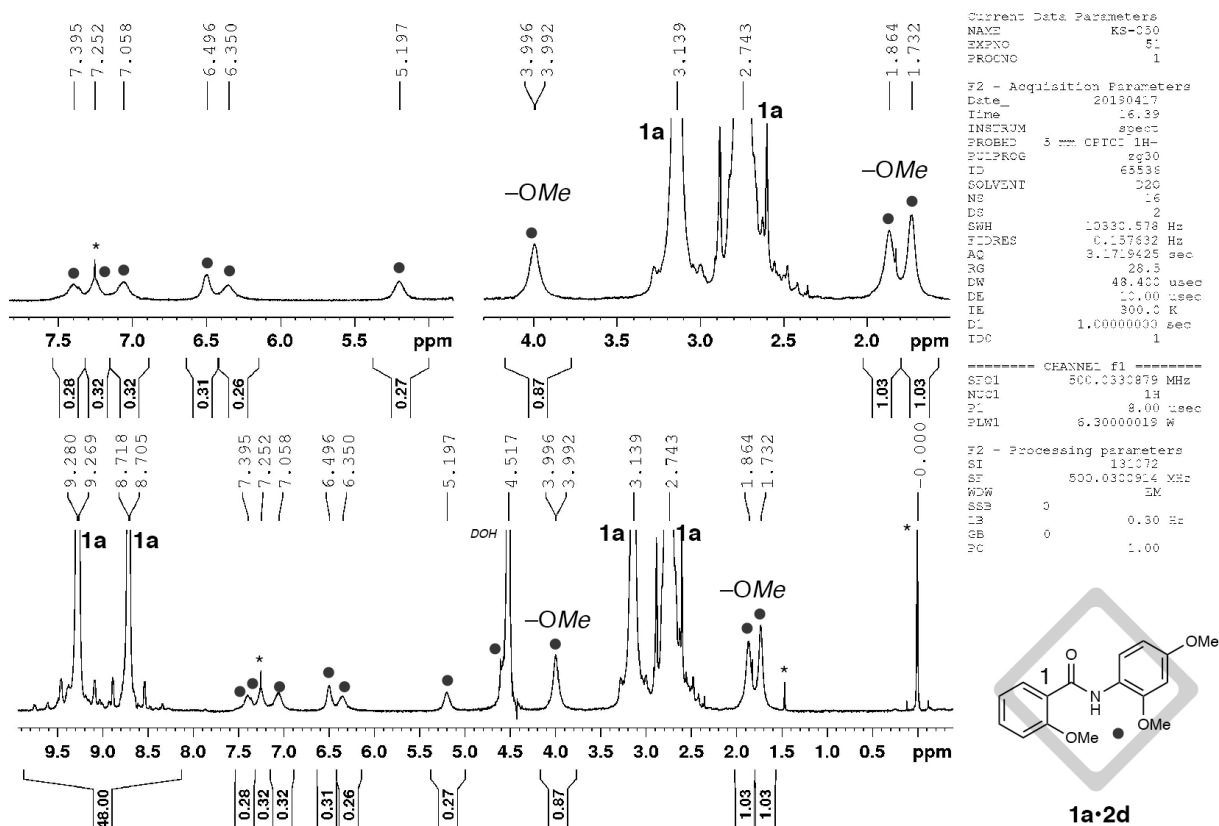
Supplementary Figure 20. ^1H - ^{13}C HSQC NMR (500 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{c})_2$.

Formation of inclusion complex **1a•2d**

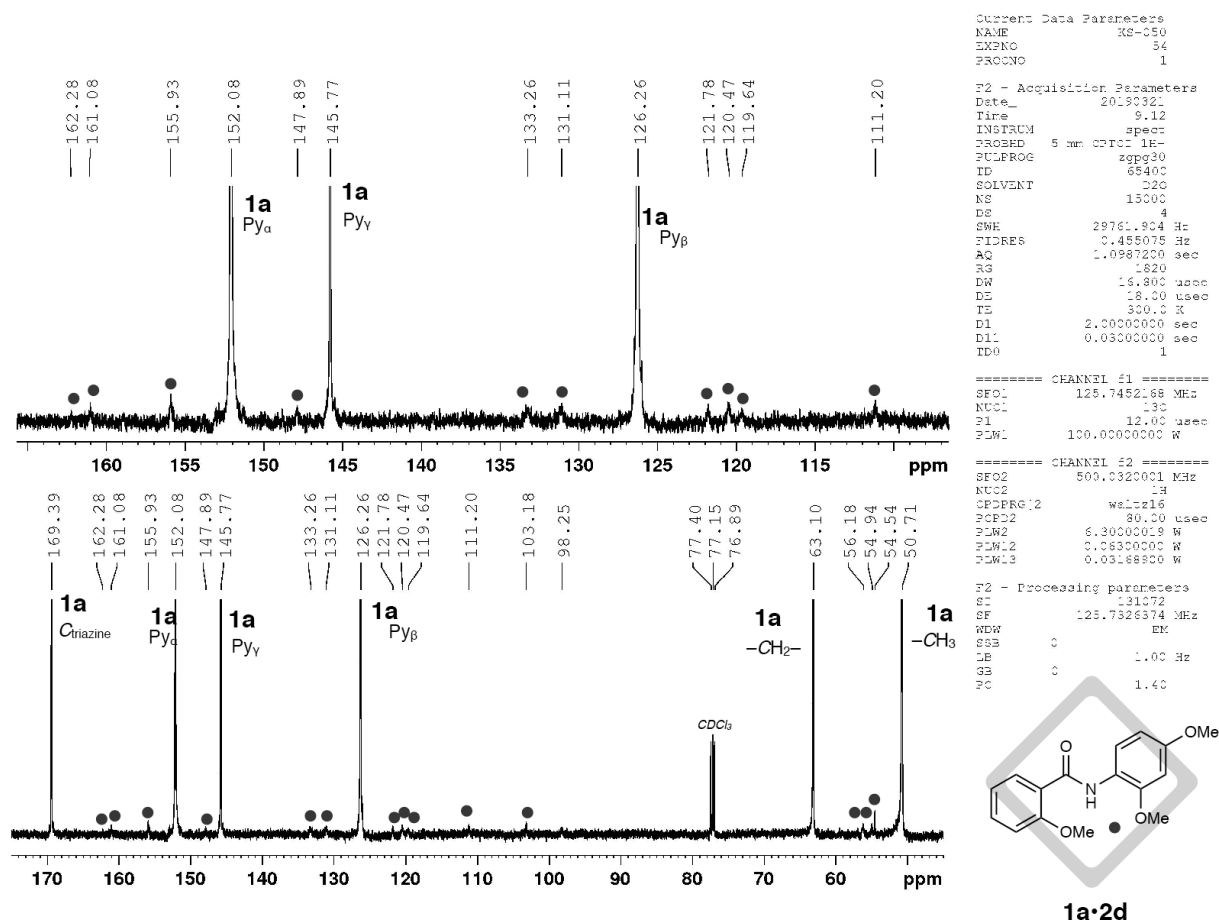


Inclusion complex **1a•2d** was formed from a mixture of **2d** (100 μmol , 5 eq.) and **1a** (20 mM, 1.0 mL) by stirring at 100 $^\circ\text{C}$ for 1 h (30% yield).

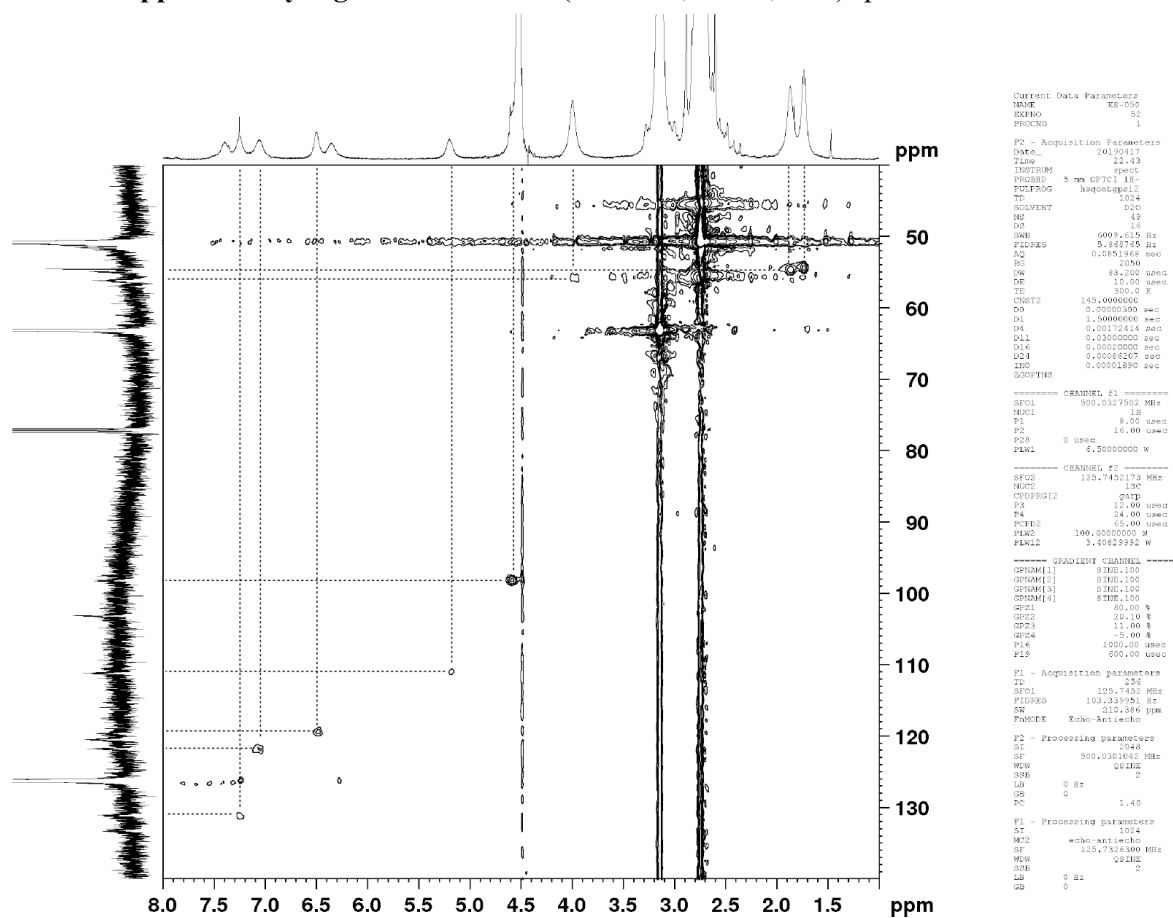
Physical data of 1a•2d: ^1H NMR (500 MHz, D_2O , 323 K): δ 1.73 (s, 3H, **2d**, $-\text{OMe}$), 1.86 (s, 3H, **2d**, $-\text{OMe}$), 2.74 (s, 72H, **1a**, CH_3), 3.14 (s, 24H, **1a**, CH_2), 3.99 (s, 3H, **2d**, $-\text{OMe}$), 4.60 (br, 1H, **2d**, ArH), 5.20 (br, 1H, **2d**, ArH), 6.35 (br, 1H, **2d**, ArH), 6.50 (br, 1H, **2d**, ArH), 7.06 (br, 1H, **2d**, ArH), 7.25 (br, 1H, **2d**, ArH), 7.40 (br, 1H, **2d**, ArH), 8.71 (d, $J = 6.0$ Hz, 24H, **1a**, PyH_β), 9.27 (d, $J = 6.0$ Hz, 24H, **1a**, PyH_α); ^{13}C NMR (125 MHz, D_2O , 323 K): δ 50.7 (**1a**, CH_3), 54.5 (**2b**, CH_3), 54.9 (**2b**, CH_3), 56.2 (**2b**, CH_3), 63.1 (**1a**, CH_2), 98.3 (**2b**, CH), 103.2 (**2b**, CH), 111.2 (**2b**, CH), 119.6 (**2b**, CH), 120.5 (**2b**, C), 121.8 (**2b**, CH), 126.3 (**1a**, Py_β), 131.1 (**2b**, CH), 133.3 (**2b**, CH), 145.8 (**1a**, Py_γ), 147.9 (**2b**, C), 152.1 (**1a**, Py_α), 155.9 (**2b**, C), 161.1 (**2b**, C), 162.3 (**2b**, C), 169.4 (**1a**, $\text{C}_{\text{triazine}}$).



Supplementary Figure 21. ^1H NMR (500 MHz, 323 K, D_2O) spectrum of **1a•2d**.

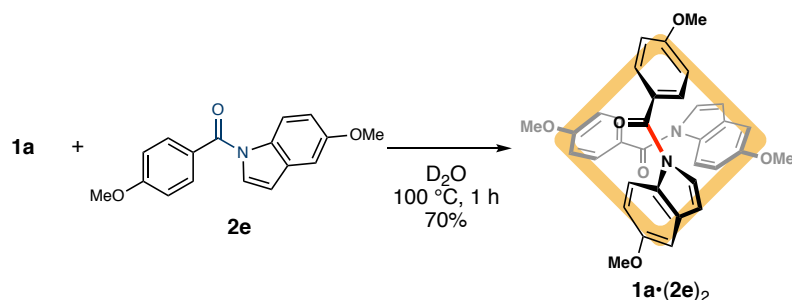


Supplementary Figure 22. ^{13}C NMR (125 MHz, 323 K, D_2O) spectrum of **1a·2d**.



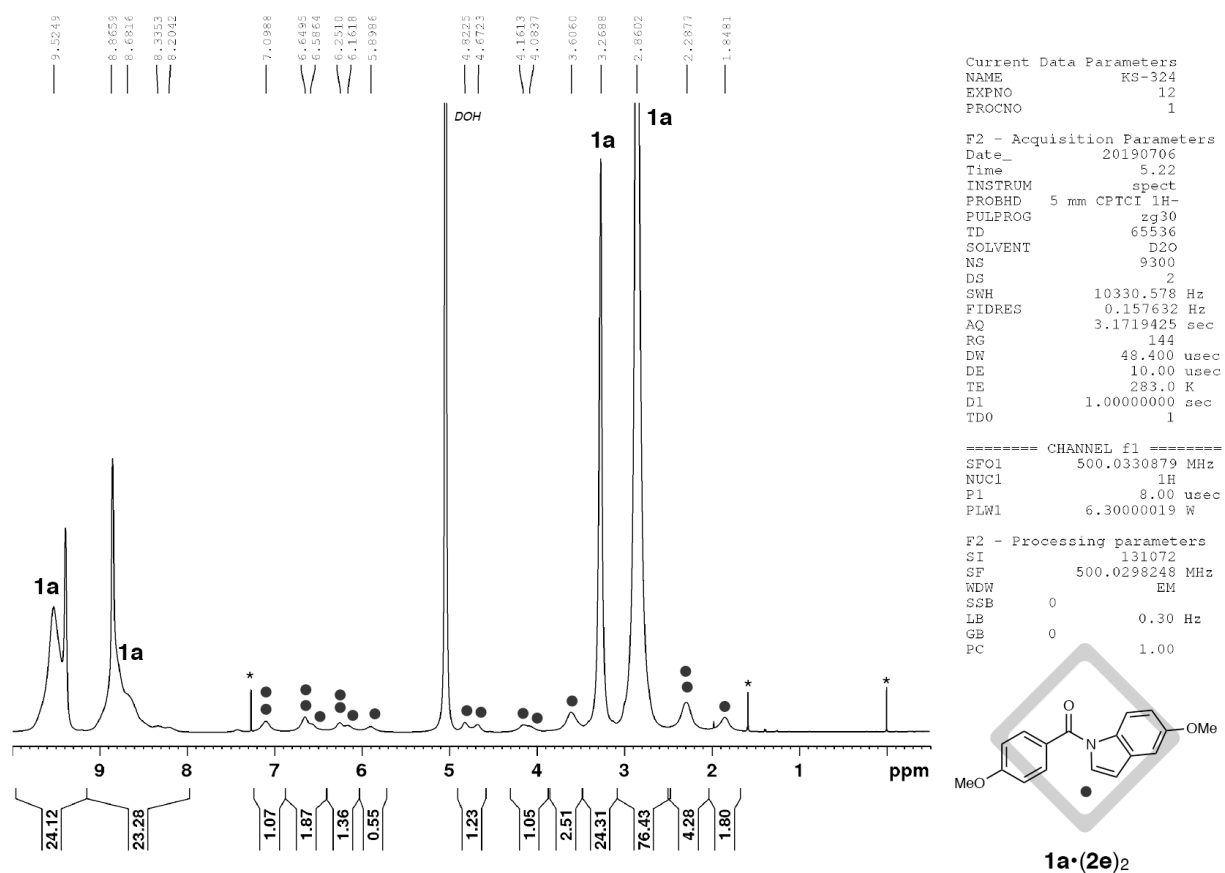
Supplementary Figure 23. ^1H - ^{13}C HSQC NMR (500 MHz, 323 K, D_2O) spectrum of **1a·2d**.

Formation of inclusion complex $1a \cdot (2e)_2$



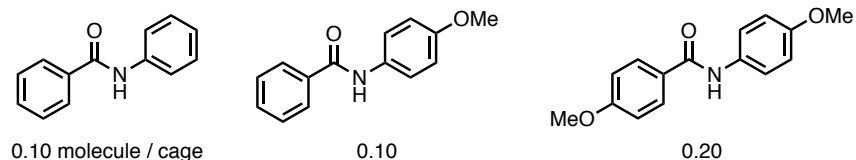
Inclusion complex $1a \cdot (2e)_2$ was formed from a mixture of **2e** (100 μmol , 5 eq.) and **1a** (20 mM, 1.0 mL) by stirring at 100 $^{\circ}\text{C}$ for 1 h (70% yield). *The severe broadening of signals precluded ^{13}C NMR characterization.*

Physical data of $1a \cdot (2e)_2$: ^1H NMR (500 MHz, D_2O , 283 K): δ 1.85 (s, 3H, **2e**, $-\text{OMe}$), 2.29 (s, 6H, **2e**, $-\text{OMe} \times 2$), 2.86 (br, 73H, **1a** and **2e**, CH_3 and ArH), 3.27 (s, 24H, **1a**, CH_2), 3.60 (s, 3H, **2e**, $-\text{OMe}$), 4.08 (br, 1H, **2e**, ArH), 4.06 (br, 1H, **2e**, ArH), 4.67 (br, 1H, **2e**, ArH), 4.83 (br, 1H, **2e**, ArH), 5.89 (br, 1H, **2e**, ArH), 6.16 (br, 1H, **2e**, ArH), 6.25 (br, 2H, **2e**, ArH), 6.58 (br, 1H, **2e**, ArH), 6.65 (br, 2H, **2e**, ArH), 7.10 (br, 2H, **2e**, ArH), 8.1–9.1 (br, 24H, PyH_β), 9.3–9.8 (br, 24H, PyH_α).



Supplementary Figure 24. ^1H NMR (500 MHz, 283 K, D_2O) spectrum of $1a \cdot (2e)_2$.

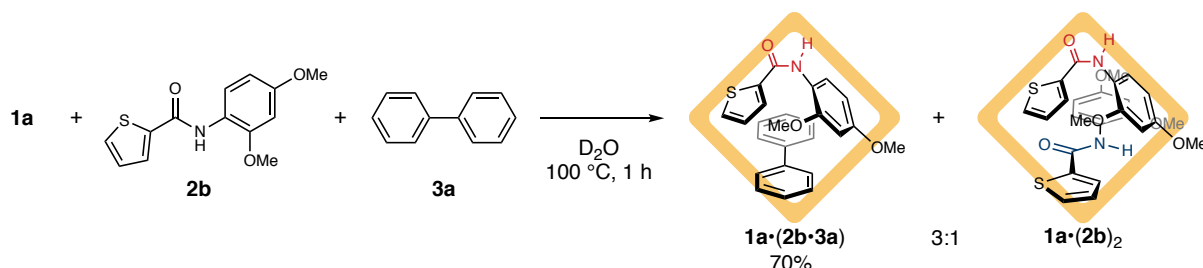
Inclusion of other amides



Supplementary Figure 25. Non-electron-rich amides which were hardly encapsulated in cage **1a**. Inclusion ratios (guest/cage) are shown in the figure.

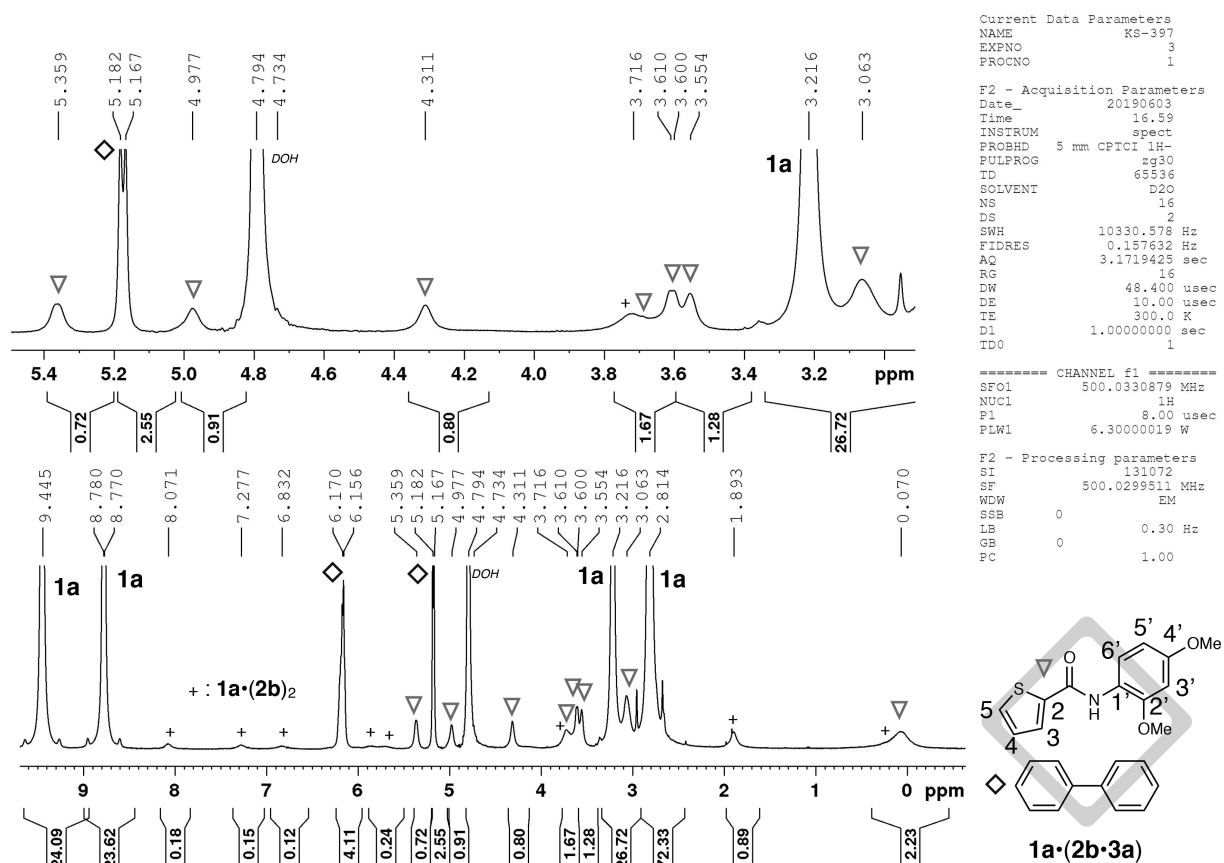
4. Formation of ternary complexes

Formation of ternary complex **1a**•(**2b**•**3a**)

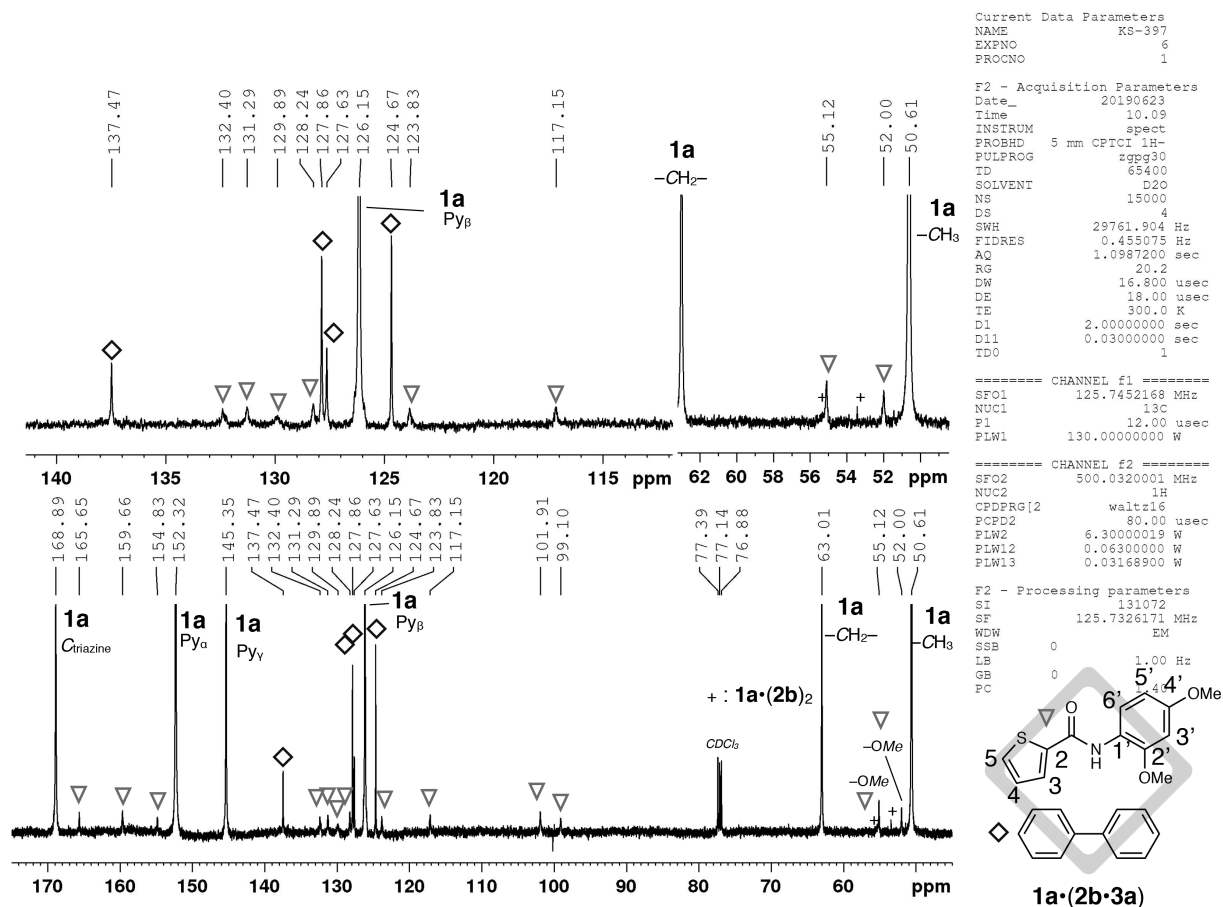


Amide **2b** (15.5 mg, 58.9 μmol) and biphenyl (**3a**, 9.41 mg, 61.0 μmol) were suspended in an aqueous solution of cage **1a** (20.0 mM, 1.0 mL) and stirred at $100\text{ }^{\circ}\text{C}$ for 1 h. After removal of residual solid by filtration, the ternary complex **1a**•(**2b**•**3a**) was obtained in 70% yield as an equilibrated mixture with **1a**•(**2b**)₂ (3:1), as confirmed by ^1H NMR spectroscopy.

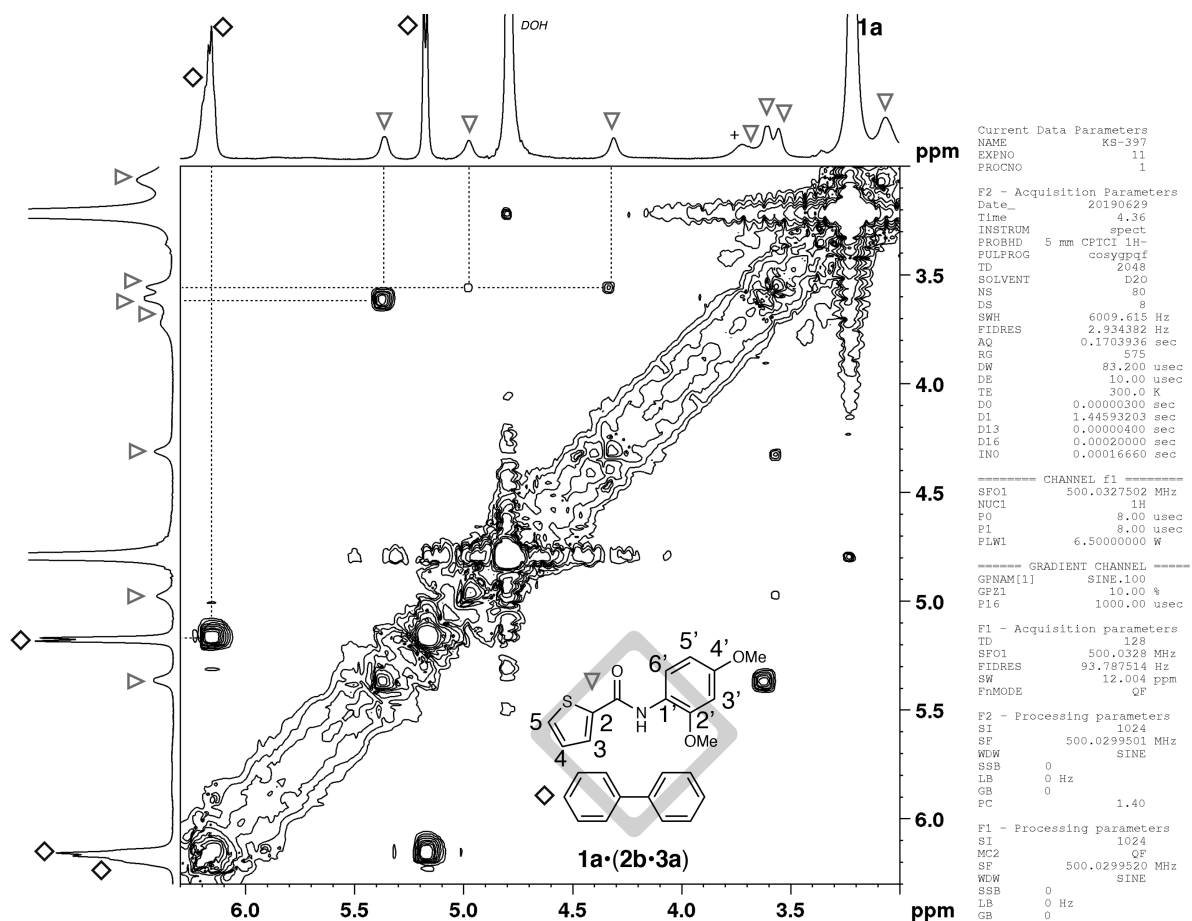
Physical data of **1a•(**2b**•**3a**):** ^1H NMR (500 MHz, D_2O , 300 K): δ 0.07 (br, 3H, **2b**, -OMe), 2.81 (s, 72H, **1a**, CH_3), 3.06 (br, 3H, **2b**, -OMe), 3.21 (s, 24H, **1a**, CH_2), 3.55 (br, 1H, **2b**, ArH), 3.60 (br, 1H, **2b**, ArH), 3.71 (br, 1H, **2b**, ArH), 4.31 (br, 1H, **2b**, ArH), 4.98 (br, 1H, **2b**, ArH), 5.17 (d, $J = 6.4\text{ Hz}$, 4H, **3a**, ArH), 5.36 (br, 1H, **2b**, ArH), 6.16 (br, 2H, **3a**, ArH), 6.17 (br, 4H, **3a**, ArH), 8.78 (br, 24H, **1a**, PyH_β), 9.44 (br, 24H, **1a**, PyH_α); ^{13}C NMR (125 MHz, D_2O , 300 K): δ 50.6 (**1a**, CH_3), 52.0 (**2b**, $-\text{OCH}_3$), 55.1 (**2b**, $-\text{OCH}_3$), 63.0 (**1a**, CH_2), 99.1 (**2b**, CH), 101.9 (**2b**, CH), 117.2 (**2b**, C), 123.8 (**2b**, CH), 124.7 (**3a**, CH), 126.2 (**1a**, Py_β), 127.6 (**3a**, CH), 127.8 (**3a**, CH), 128.2 (**2b**, CH), 129.9 (**2b**, CH), 131.3 (**2b**, CH), 132.4 (**2b**, C), 137.5 (**3a**, C), 145.4 (**1a**, Py_γ), 152.3 (**1a**, Py_α), 154.8 (**2b**, C), 159.7 (**2b**, C), 165.7 (**2b**, C), 168.9 (**1a**, $\text{C}_{\text{triazine}}$).



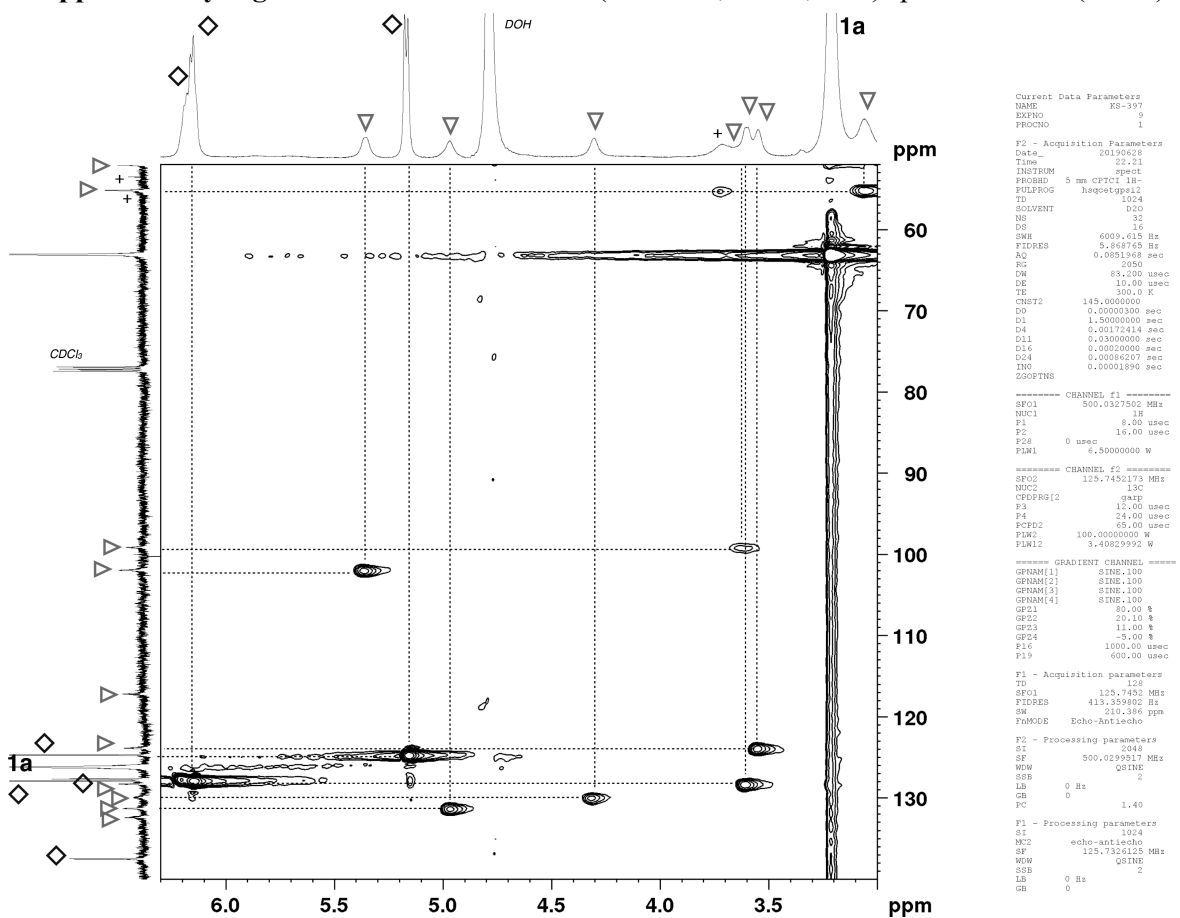
Supplementary Figure 26. ^1H NMR (500 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{b}\cdot 3\text{a})$.



Supplementary Figure 27. ^{13}C NMR (125 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{b}\cdot 3\text{a})$.

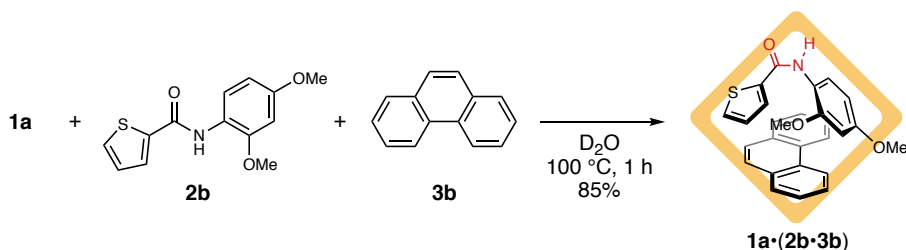


Supplementary Figure 28. ^1H - ^1H COSY NMR (500 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{b}\cdot 3\text{a})$.



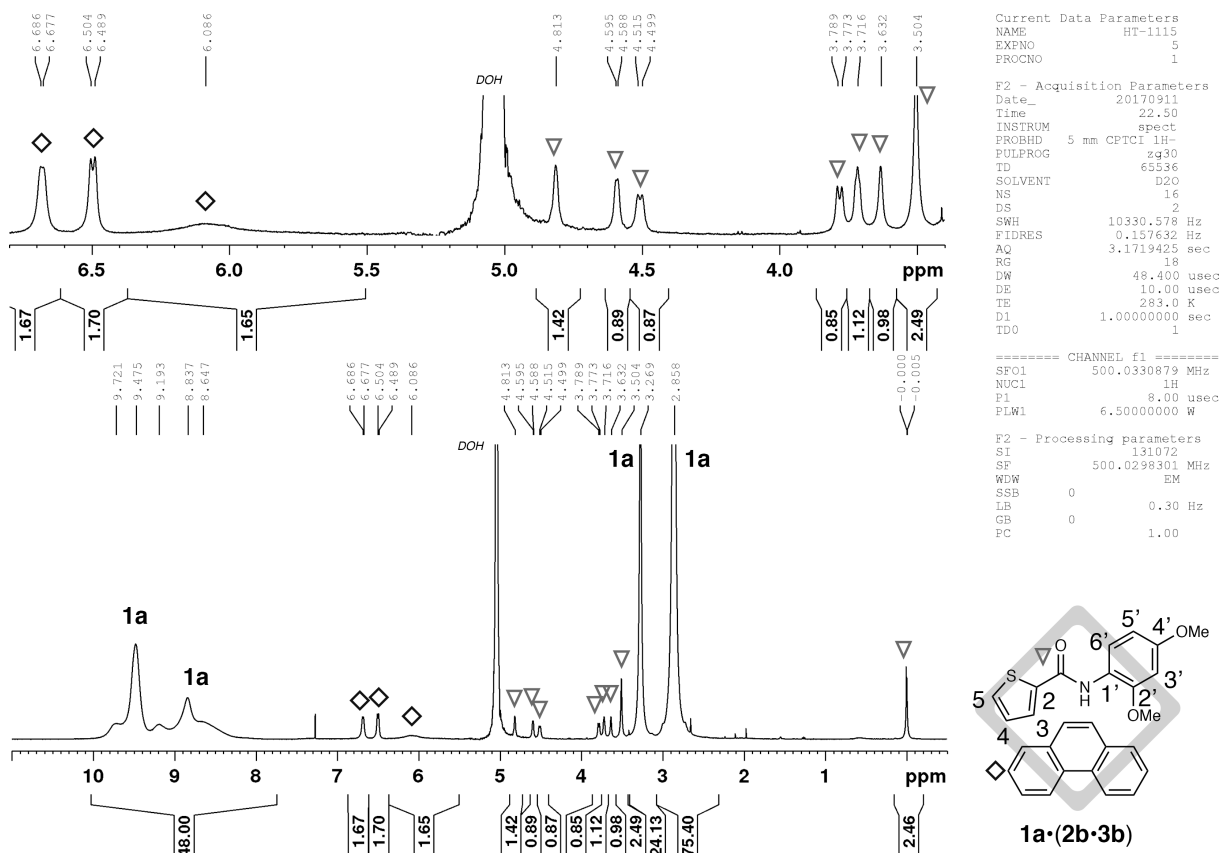
Supplementary Figure 29. ^1H - ^{13}C HSQC NMR (500 MHz, 300 K, D_2O) spectrum of $1\text{a}\cdot(2\text{b}\cdot 3\text{a})$.

Formation of ternary complex 1a•(2b•3b)

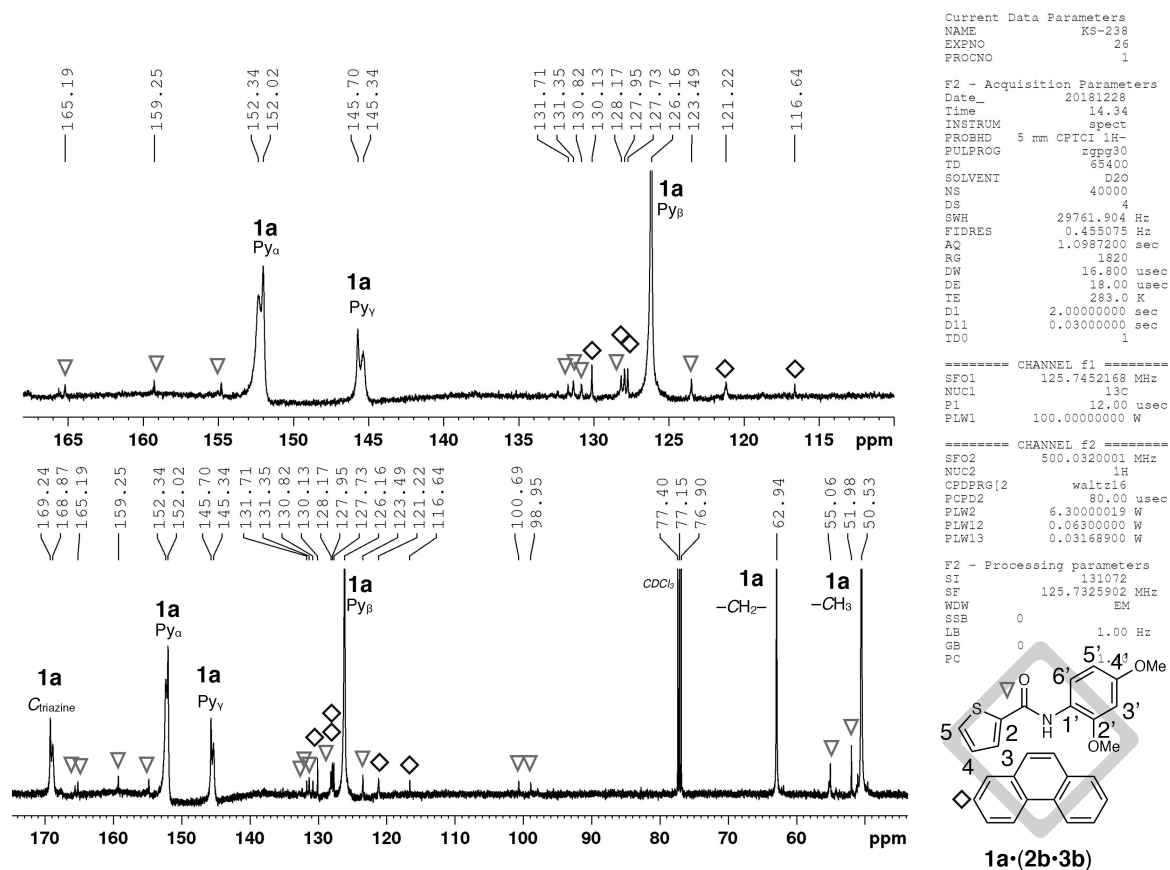


Amide **2b** (15.5 mg, 58.9 μmol) and phenanthrene (**3b**, 11.0 mg, 61.7 μmol) were suspended in an aqueous solution of cage **1a** (20.0 mM, 1.0 mL) and stirred at 100 $^{\circ}\text{C}$ for 1 h. After removal of residual solid by filtration, the ternary complex **1a•(2b•3b)** was obtained in 85% yield as confirmed by ^1H NMR spectroscopy.

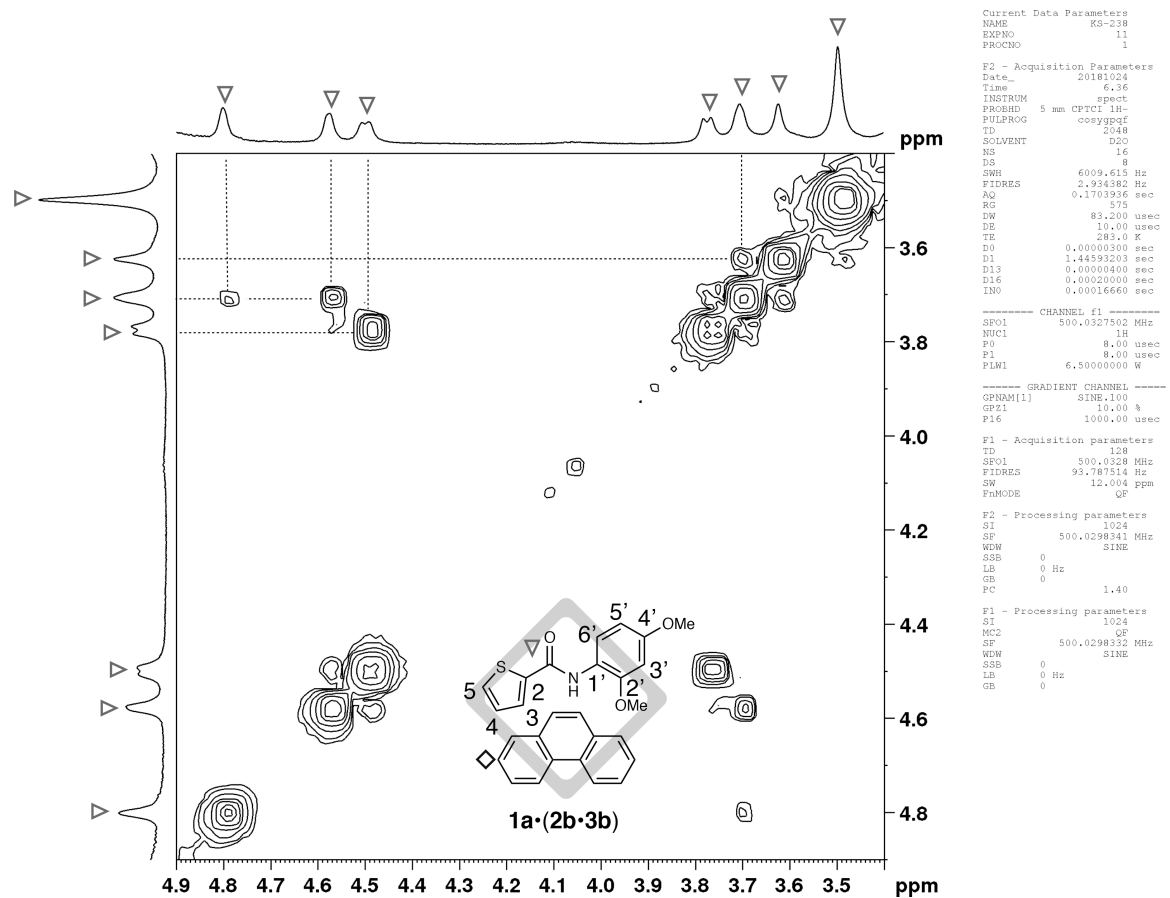
Physical data of 1a•(2b•3b): ^1H NMR (500 MHz, D_2O , 283 K): δ -0.01 (s, 3H, **2b**, -OMe), 2.86 (s, 72H, **1a**, CH_3), 3.27 (s, 24H, **1a**, CH_2), 3.50 (s, 3H, **2b**, -OMe), 3.63 (br, 1H, **2b**, ArH), 3.72 (br, 1H, **2b**, ArH), 3.78 (d, $J = 8.0$ Hz, 1H, **2b**, ArH), 4.50 (d, $J = 7.0$ Hz, 1H, **2b**, ArH), 4.59 (br, 1H, **2b**, ArH), 4.81 (br, 1H, **2b**, ArH), 6.09 (br, 2H, **3b**, ArH), 6.49 (d, $J = 8.5$ Hz, 2H, **3b**, ArH), 6.68 (br, 2H, **3b**, ArH), 8.2–9.8 (brm, 48H, **1a**, $\text{PyH}_\beta/\text{PyH}_\alpha$); ^{13}C NMR (125 MHz, D_2O , 283 K): δ = 50.5 (**1a**, CH_3), 52.0 (**2b**, CH_3), 55.1 (**2b**, CH_3), 62.9 (**1a**, CH_2), 99.0 (**2b**, CH), 100.7 (**2b**, CH), 116.6 (**3b**, C), 121.2 (**3b**, CH), 123.5 (**2b**, CH), 126.2 (**1a**, Py_β), 127.7 (**3b**, C), 128.0 (**3b**, CH), 128.2 (**2b**, CH), 130.1 (**3b**, CH), 130.8 (**2b**, CH), 131.4 (**2b**, CH), 131.7 (**2b**, C), 145.3 (**1a**, Py_γ), 145.7 (**1a**, Py_γ), 152.0 (**1a**, Py_α), 152.3 (**1a**, Py_α), 154.8 (**2b**, C), 159.3 (**2b**, C), 165.2 (**2b**, C), 168.9 (**1a**, $\text{C}_{\text{triazine}}$), 169.2 (**1a**, $\text{C}_{\text{triazine}}$).



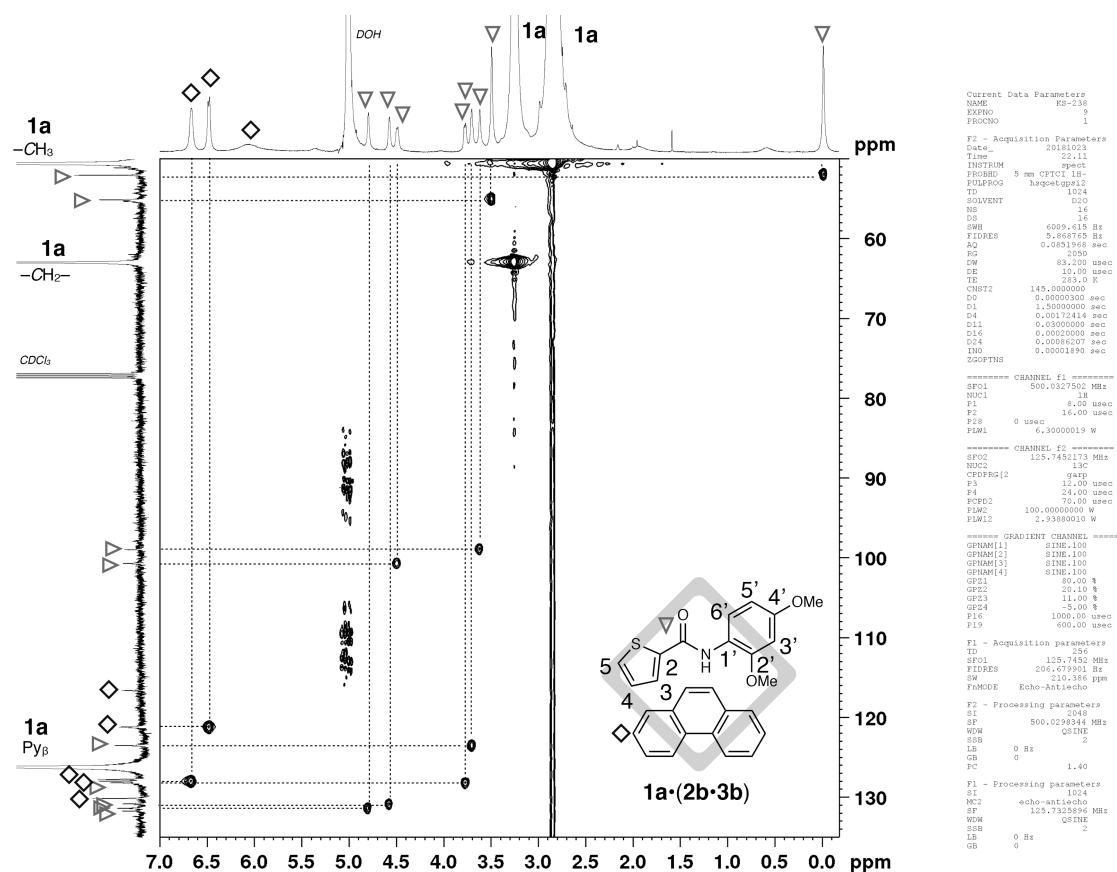
Supplementary Figure 30. ^1H NMR (500 MHz, 283 K, D_2O) spectrum of **1a•(2b•3b)**.



Supplementary Figure 31. ¹³C NMR (125 MHz, 283 K, D₂O) spectrum of 1a•(2b•3b).

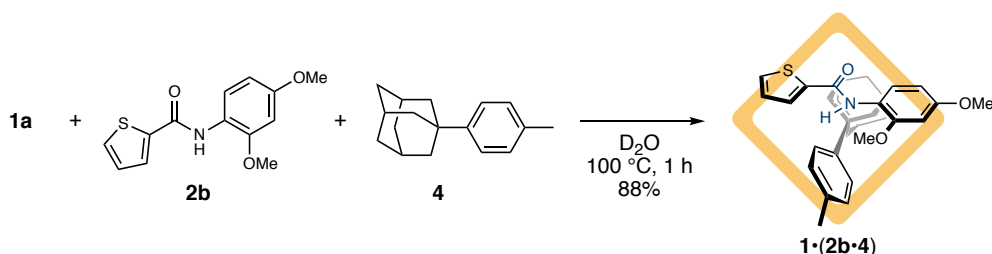


Supplementary Figure 32. ¹H-¹H COSY NMR (500 MHz, 283 K, D₂O) spectrum of 1a•(2b•3b).



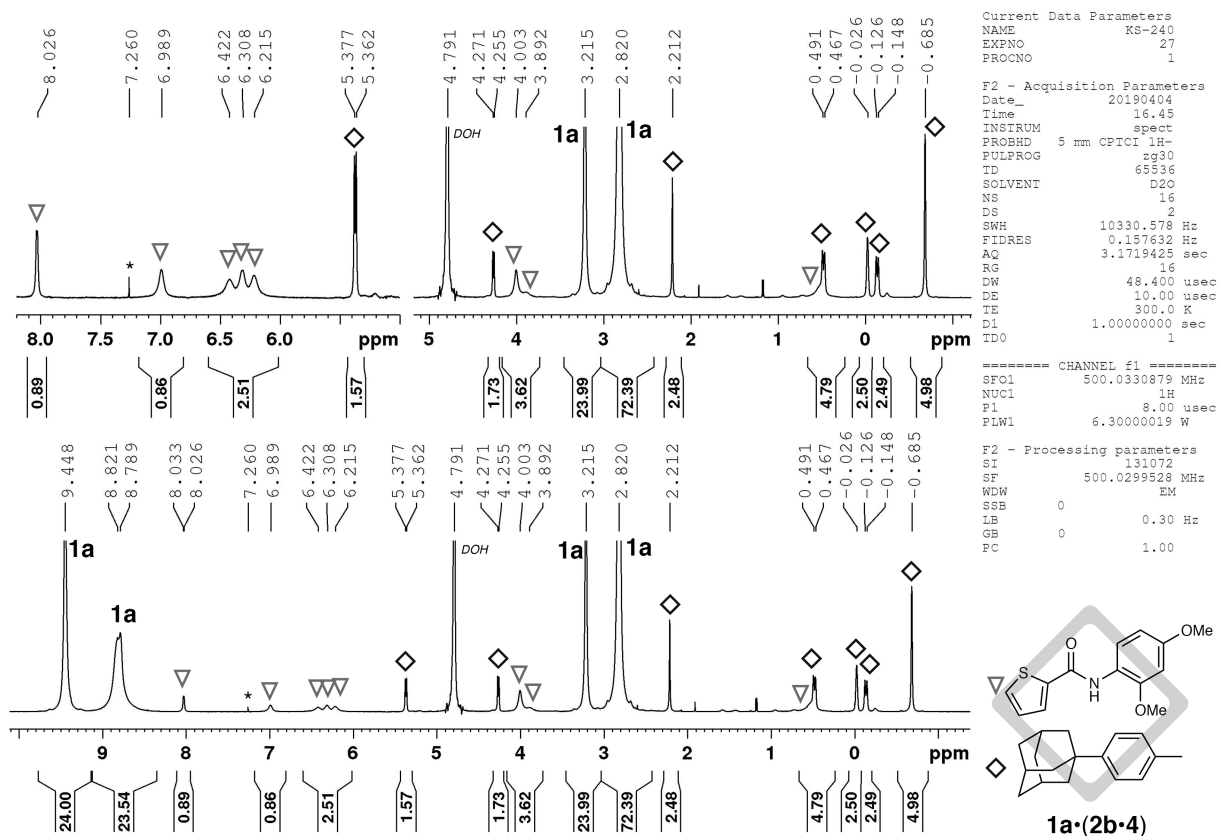
Supplementary Figure 33. ^1H - ^{13}C HSQC NMR (500 MHz, 283 K, D_2O) spectrum of $1\mathbf{a}\cdot(2\mathbf{b}\cdot 3\mathbf{b})$.

Formation of ternary complex $1\mathbf{a}\cdot(2\mathbf{b}\cdot 4)$

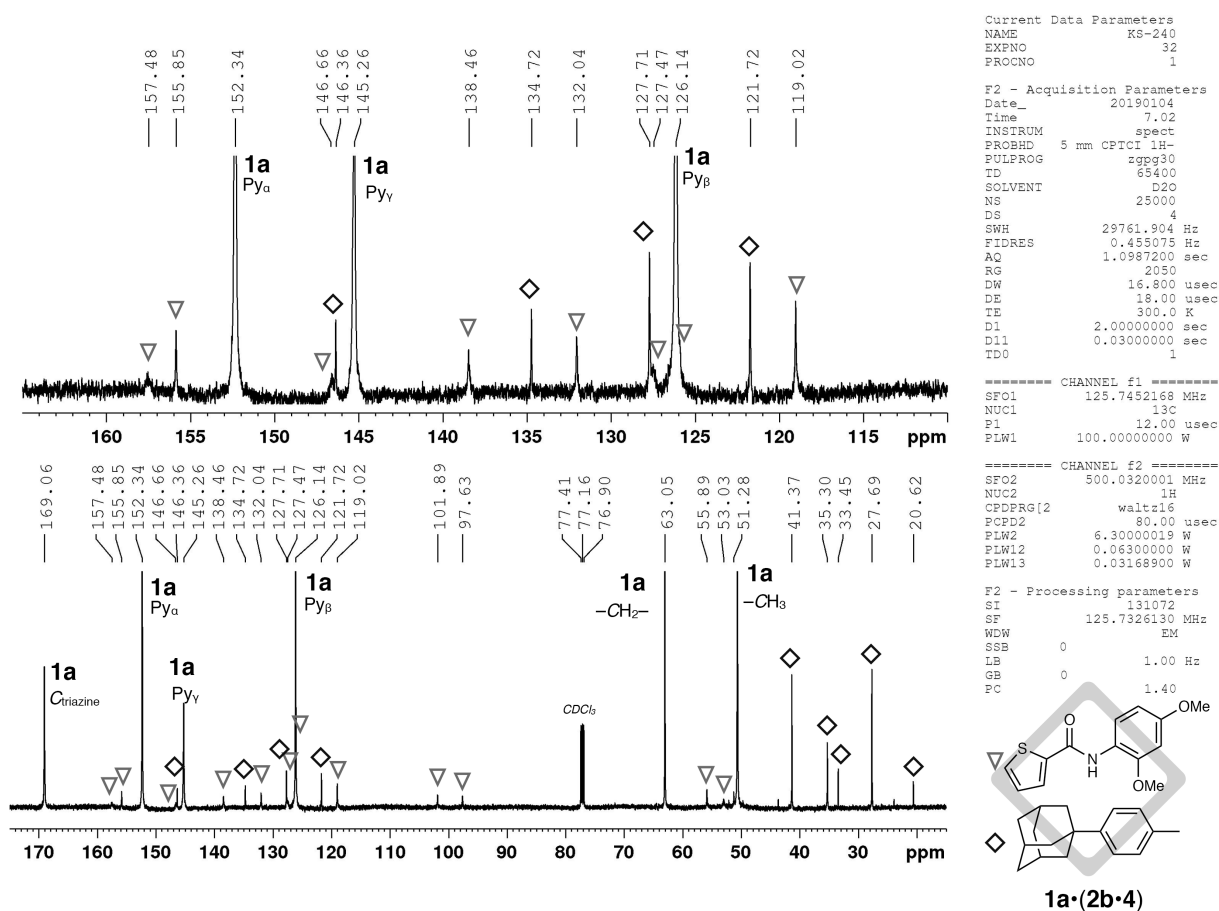


Inclusion complex $1\mathbf{a}\cdot(2\mathbf{b}\cdot 4)$ was formed from a mixture of $2\mathbf{b}$ (58.9 μmol , 3 eq.), 4 (58.8 μmol , 3 eq.) and $1\mathbf{a}$ (20 mM, 1.0 mL) by stirring at 100 $^\circ\text{C}$ for 1 h (88% yield).

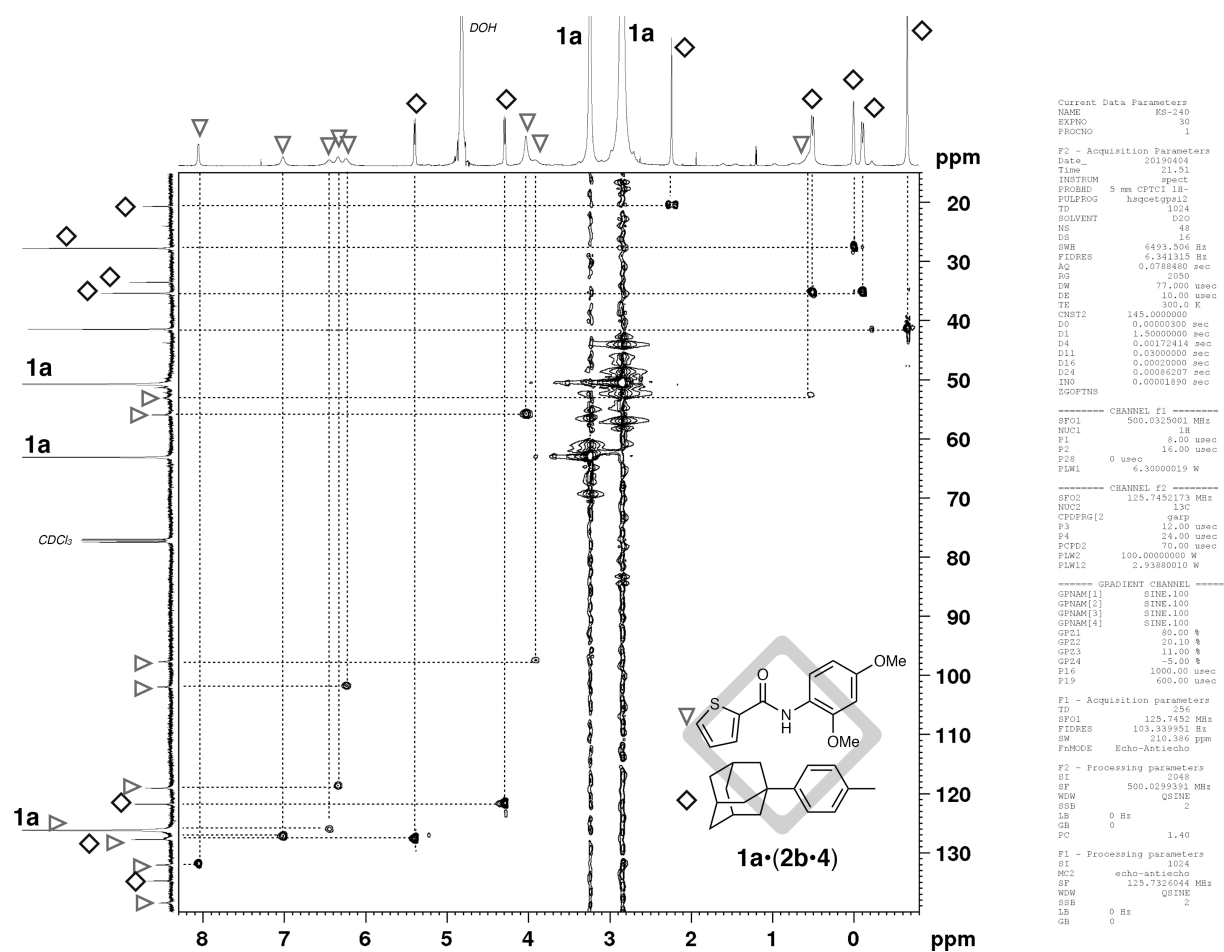
Physical data of $1\mathbf{a}\cdot(2\mathbf{d}\cdot 4)$: ^1H NMR (500 MHz, D_2O , 300 K): δ -0.68 (s, 6H, 4 , CH_2), -0.14 (d, J = 11.0 Hz, 3H, 4 , CH_2), -0.03 (s, 3H, 4 , CH), 0.48 (d, J = 12.0 Hz, 3H, 4 , CH_2), 0.53 (s, 3H, $2\mathbf{b}$, -OMe), 2.21 (s, 3H, 4 , -Me), 2.82 (s, 72H, $1\mathbf{a}$, CH_3), 3.22 (s, 24H, $1\mathbf{a}$, CH_2), 3.89 (br, 1H, $2\mathbf{b}$, ArH), 4.00 (s, 3H, $2\mathbf{b}$, -OMe), 4.26 (d, J = 8.0 Hz, 2H, 4 , ArH), 5.37 (d, J = 7.5 Hz, 2H, 4 , ArH), 6.22 (br, 1H, $2\mathbf{b}$, ArH), 6.31 (br, 1H, $2\mathbf{b}$, ArH), 6.42 (br, 1H, $2\mathbf{b}$, ArH), 6.99 (br, 1H, $2\mathbf{b}$, ArH), 8.03 (br, 1H, $2\mathbf{b}$, ArH); ^{13}C NMR (125 MHz, D_2O , 300 K): δ 20.6 (4 , CH_3), 27.7 (4 , CH), 33.5 (4 , C), 35.3 (4 , CH_2), 41.4 (4 , CH_2), 51.3 ($1\mathbf{a}$, CH_3), 53.0 ($2\mathbf{b}$, CH_3), 55.9 ($2\mathbf{b}$, CH_3), 63.1 ($1\mathbf{a}$, CH_2), 97.6 ($2\mathbf{b}$, CH), 101.9 ($2\mathbf{b}$, CH), 119.0 ($2\mathbf{b}$, CH), 121.7 (4 , CH), 126.1 ($1\mathbf{a}$, Py_β , $2\mathbf{b}$, CH), 127.5 ($2\mathbf{b}$, CH), 127.7 (4 , CH), 132.0 ($2\mathbf{b}$, CH), 134.7 (4 , C), 138.5 ($2\mathbf{b}$, C), 145.3 ($1\mathbf{a}$, Py_γ), 146.4 (4 , C), 146.7 ($2\mathbf{b}$, C), 152.3 ($1\mathbf{a}$, Py_α), 155.9 ($2\mathbf{b}$, C), 157.5 ($2\mathbf{b}$, C), 169.1 ($1\mathbf{a}$, $\text{C}_{\text{triazine}}$).



Supplementary Figure 34. ^1H NMR (500 MHz, 300 K, D_2O) spectrum of 1a•(2b•4).



Supplementary Figure 35. ^{13}C NMR (125 MHz, 300 K, D_2O) spectrum of 1a•(2b•4).



Supplementary Figure 36. ^1H - ^{13}C HSQC NMR (500 MHz, 300 K, D_2O) spectrum of **1a•(2b•4)**.

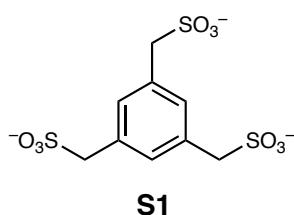
5. X-ray crystallographic analyses of inclusion complexes

General procedure for crystallization

An aqueous solution (ca. 0.5 mL) of an inclusion complex ($[1a] = 20$ mM or $[1b] = 5.0$ mM) was stood at room temperature and water solvent was allowed to evaporate. After one week, a single crystal suitable for X-ray diffraction analysis was obtained.

Crystallization of $1b \cdot (2e)_2$ for the X-ray crystallographic analysis

To an aqueous solution (ca. 0.5 mL) of inclusion complex $1b \cdot (2e)_2$ ($[1b] = 5.0$ mM) was added co-crystallization reagent **S1**•3Na (ca. 1 mg). The resulted precipitate was dissolved upon heating at 100 °C to afford a clear yellow solution. The solution was then stood at 50 °C and water solvent was allowed to evaporate. After one week, a single crystal suitable for X-ray diffraction analysis was obtained.



Note: In some cases, the occupancy of the amide guest is not consistent with the observed stoichiometry in 1H NMR. This is probably caused by dynamic guest motion, rapid guest exchange in the solution during the crystallization.

Supplementary Table 1 | Crystal data and structural refinement for **1b•(2a)₂**, **1a•(2b)₂**, **1a•(2b•3a)**, **1a•(2b•4)**, **1a•(2c)₂**, **1a•2d** and **1a•(2e)₂**

	1b•(2a)₂	1a•(2b)₂	1a•(2b•3a)	1a•(2b•4)
Identification code	ht892	ks29-3	ks397-2_2	ks240_2
CCDC number	1949143	1949144	1949145	1949146
Empirical formula	C ₁₆₄ H ₁₃₀ N _{46.31} O _{110.10} Pd ₆	C ₁₂₁ H ₁₅₇ N _{40.45} O _{47.89} Pd _{5.99} S	C _{120.50} H ₁₅₆ N _{39.35} O _{42.11} Pd ₆ S _{0.50}	C ₁₃₈ H _{178.40} N _{47.15} O _{71.88} Pd ₆ S
Formula weight	5149.44	3613.84	3483.92	4318.35
Temperature	90(2) K	90(2) K	90(2) K	90(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Tetragonal	Triclinic	Triclinic	Triclinic
Space group	<i>P</i> 4 ₁ 2 ₁ 2	<i>P</i> −1	<i>P</i> −1	<i>P</i> −1
Unit cell dimensions	<i>a</i> = <i>b</i> = 30.657(6) Å <i>c</i> = 29.219(5) Å <i>α</i> = <i>β</i> = <i>γ</i> = 90°	<i>a</i> = 27.464(11) Å <i>b</i> = 27.612(11) Å <i>c</i> = 32.441(13) Å <i>α</i> = 100.596(5)° <i>β</i> = 91.868(5)° <i>γ</i> = 107.026(5)°	<i>a</i> = 27.6373(13) Å <i>b</i> = 27.6066(13) Å <i>c</i> = 32.1213(15) Å <i>α</i> = 101.0770(10)° <i>β</i> = 91.7580(10)° <i>γ</i> = 107.2910(10)°	<i>a</i> = 24.220(3) Å <i>b</i> = 24.463(3) Å <i>c</i> = 24.640(3) Å <i>α</i> = 112.3955(12)° <i>β</i> = 119.2688(12)° <i>γ</i> = 91.5515(13)°
Volume	27461(11) Å ³	23024(16) Å ³	22639.8(19) Å ³	11356(2) Å ³
<i>Z</i>	4	4	4	2
Density (calculated)	1.246 Mg/m ³	1.043 Mg/m ³	1.022 Mg/m ³	1.263 Mg/m ³
Absorption coefficient	0.475 mm ^{−1}	0.530 mm ^{−1}	0.531 mm ^{−1}	0.557 mm ^{−1}
<i>F</i> (000)	10380	7363	7101	4407
Crystal size	0.17 × 0.14 × 0.10 mm ³	0.12 × 0.11 × 0.09 mm ³	0.18 × 0.12 × 0.09 mm ³	0.35 × 0.29 × 0.19 mm ³
Theta range for data	1.170 to 27.134°	1.053 to 25.141°	0.649 to 25.028°	0.933 to 28.984°
Index ranges	−39 ≤ <i>h</i> ≤ 39, −39 ≤ <i>k</i> ≤ 39, −37 ≤ <i>l</i> ≤ 37	−32 ≤ <i>h</i> ≤ 32, −32 ≤ <i>k</i> ≤ 32, −38 ≤ <i>l</i> ≤ 38	−32 ≤ <i>h</i> ≤ 32, −32 ≤ <i>k</i> ≤ 32, −38 ≤ <i>l</i> ≤ 38	−32 ≤ <i>h</i> ≤ 32, −32 ≤ <i>k</i> ≤ 33, −33 ≤ <i>l</i> ≤ 32
Reflection collected	309355	225659	225106	135036
Independent reflections	30358 [<i>R</i> _{int} = 0.0909]	81687 [<i>R</i> _{int} = 0.0614]	79841 [<i>R</i> _{int} = 0.0797]	54593 [<i>R</i> _{int} = 0.0253]
Completeness	100.0 % (<i>θ</i> = 25.242°)	99.2 % (<i>θ</i> = 25.141°)	99.8% (<i>θ</i> = 25.028°)	99.6% (<i>θ</i> = 25.242°)
Max. and min. transmission	0.7455 and 0.6918	0.7452 and 0.698	0.7454 and 0.6891	0.7458 and 0.6501
Refinement method	Full-matrix least-squares on <i>F</i> ²			
Data / restraints / parameters	93211 / 356 / 1609	81687 / 1582 / 3896	79841 / 1062 / 3666	54593 / 1574 / 3075
Goodness-of-fit on <i>F</i> ²	1.066	1.049	1.034	1.409
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0656, <i>wR</i> ₂ = 0.1715	<i>R</i> ₁ = 0.0947, <i>wR</i> ₂ = 0.2883	<i>R</i> ₁ = 0.1026, <i>wR</i> ₂ = 0.2998	<i>R</i> ₁ = 0.1050, <i>wR</i> ₂ = 0.3137
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0997, <i>wR</i> ₂ = 0.1960	<i>R</i> ₁ = 0.1531, <i>wR</i> ₂ = 0.3162	<i>R</i> ₁ = 0.1701, <i>wR</i> ₂ = 0.3338	<i>R</i> ₁ = 0.1392, <i>wR</i> ₂ = 0.3588
Largest diff. peak and hole	0.912 and −0.537 e•Å ^{−3}	1.470 and −0.897 e•Å ^{−3}	1.462 and −1.106 e•Å ^{−3}	4.533 and −1.711 e•Å ^{−3}

Supplementary Table 1 | (continued)

	1a•(2c)₂	1a•2d	1a•(2e)₂•S1
Identification code	ks27_2	ks50-2_2	ht1350b_2
CCDC number	1949149	1949150	1949151
Empirical formula	C ₁₂₁ H _{156.50} N _{42.50} O _{49.25} Pd ₆	C _{116.99} H _{146.94} N _{41.21} O _{56.33} Pd ₆	C _{188.50} H _{147.83} N ₃₉ O _{67.98} Pd ₆ S _{7.50}
Formula weight	3632.78	3670.13	4925.85
Temperature	90(2) K	100(2) K	90(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Triclinic	Triclinic	Triclinic
Space group	<i>P</i> −1	<i>P</i> −1	<i>P</i> −1
Unit cell dimensions	<i>a</i> = 27.385(5) Å <i>b</i> = 27.601(5) Å <i>c</i> = 32.376(6) Å <i>α</i> = 100.807(2)° <i>β</i> = 91.937(2)° <i>γ</i> = 106.917(2)°	<i>a</i> = 27.3220(15) Å <i>b</i> = 27.6097(15) Å <i>c</i> = 32.1364(18) Å <i>α</i> = 100.3850(13)° <i>β</i> = 92.5096(13)° <i>γ</i> = 107.2175(12)°	<i>a</i> = 20.188(2) Å <i>b</i> = 21.563(3) Å <i>c</i> = 32.165(4) Å <i>α</i> = 74.207(2)° <i>β</i> = 78.655(2)° <i>γ</i> = 66.230(2)°
Volume	22896(7) Å ³	22654(2) Å ³	12270(2) Å ³
<i>Z</i>	4	4	2
Density (calculated)	1.054 Mg/m ³	1.076 Mg/m ³	1.333 Mg/m ³
Absorption coefficient	0.526 mm ^{−1}	0.534 mm ^{−1}	0.577 mm ^{−1}
<i>F</i> (000)	7400	7456	4983
Crystal size	0.33 × 0.15 × 0.09 mm ³	0.28 × 0.13 × 0.10 mm ³	0.26 × 0.13 × 0.11 mm ³
Theta range for data	0.643 to 29.017°	0.784 to 24.407°	0.661 to 25.187°
Index ranges	−36 ≤ <i>h</i> ≤ 35, −37 ≤ <i>k</i> ≤ 36, −41 ≤ <i>l</i> ≤ 43	−31 ≤ <i>h</i> ≤ 31, −32 ≤ <i>k</i> ≤ 32, −37 ≤ <i>l</i> ≤ 37	−24 ≤ <i>h</i> ≤ 23, −25 ≤ <i>k</i> ≤ 25, −38 ≤ <i>l</i> ≤ 38
Reflection collected	278487	272218	121085
Independent reflections	110247 [<i>R</i> _{int} = 0.0298]	74531 [<i>R</i> _{int} = 0.0382]	43468 [<i>R</i> _{int} = 0.0514]
Completeness	99.7% (<i>θ</i> = 25.242°)	100.0% (<i>θ</i> = 24.407°)	98.4 % (<i>θ</i> = 25.187°)
Max. and min. transmission	0.7458 and 0.6734	0.7452 and 0.6767	0.7452 and 0.6637
Refinement method	Full-matrix least-squares on <i>F</i> ²		
Data / restraints / parameters	110247 / 1445 / 3701	74531 / 1010 / 4208	43468 / 2306 / 3865
Goodness-of-fit on <i>F</i> ²	1.258	1.400	1.294
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.1091, <i>wR</i> ₂ = 0.3283	<i>R</i> ₁ = 0.1082, <i>wR</i> ₂ = 0.3193	<i>R</i> ₁ = 0.1138, <i>wR</i> ₂ = 0.3264
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.1513, <i>wR</i> ₂ = 0.3607	<i>R</i> ₁ = 0.1294, <i>wR</i> ₂ = 0.3454	<i>R</i> ₁ = 0.1847, <i>wR</i> ₂ = 0.3835
Largest diff. peak and hole	3.036 and −1.820 e•Å ^{−3}	4.008 and −1.372 e•Å ^{−3}	1.721 and −0.855 e•Å ^{−3}

A- and B-level alerts in the Checkcif files:

1b•(2a)₂ (ht892)

“PLAT430_ALERT_2_A Short Inter D...A Contact O5W ..O62W 2.33 Ang. Check”

Some of the water molecules and anions are highly disordered.

“PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?) O21W Check”

The hydrogen atoms could not be located on the water molecules.

“PLAT601_ALERT_2_B Structure Contains Solvent Accessible VOIDS of . 182 Ang**3”

The crystal has voids filled with severely disordered anions and water molecules.

“PLAT934_ALERT_3_B Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 3 Check”

This alert was presumably derived from the poorly modeled diffractions, but the number is considerably small compared with the number of used reflections.

1a•(2b)₂ (ks29-3)

“PLAT430_ALERT_2_A Short Inter D...A Contact S1Y ..O43 2.80 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT602_ALERT_2_A VERY LARGE Solvent Accessible VOID(S) in Structure ! Info”

The crystal has large voids filled with severely disordered anions, water molecules and possibly disordered guest molecules with low occupancy. SQUEEZE procedure was used to deal with such molecules.

“PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 29 Check”

This alert was derived from low quality of data, possibly due to poorly modeled disordered solvent molecules and anions. It seems not a serious problem because the number of the problematic reflections is ignorable compared to that of the reflections used in the refinement (> 80000).

“PLAT201_ALERT_2_B Isotropic non-H Atoms in Main Residue(s) 9 Report”

These alerts were derived from solvent molecules/anions and TMEDA ligands of the cages, which were highly disordered.

These parts were refined isotropically.

“PLAT220_ALERT_2_B Non-Solvent Resd 1 C Ueq(max)/Ueq(min) Range 6.3 Ratio”

These alerts were due to the disordered TMEDA ligands of the cages or terminal moieties of the guest molecules.

“PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of C4A3 Check”

These alerts were derived from TMEDA ligands of the cages, which were highly disordered.

“PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of N4A1 Check”

These alerts were derived from TMEDA ligands of the cages, which were highly disordered.

“PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?) O49 Check”

The hydrogen atoms could not be located on the water molecules.

“PLAT430_ALERT_2_B Short Inter D...A Contact O1 ..O108 . 2.58 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

1a•(2b•3a) (ks397-2_2)

“PLAT430_ALERT_2_A Short Inter D...A Contact O1C ..O122 2.51 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT602_ALERT_2_A VERY LARGE Solvent Accessible VOID(S) in Structure ! Info”

The crystal has large voids filled with severely disordered anions, water molecules and possibly disordered guest molecules with low occupancy. SQUEEZE procedure was used to deal with such molecules.

“PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 27 Check”

This alert was derived from low quality of data, possibly due to poorly modeled disordered solvent molecules and anions. It seems not a serious problem because the number of the problematic reflections is ignorable compared to that of the reflections used in the refinement (> 79000).

1a•(2b•4) (ks240_2)

“PLAT430_ALERT_2_A Short Inter D...A Contact O2L ..O26 2.32 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 21 Check”

This alert was derived from low quality of data, possibly due to the saturated reflections or poorly modeled disordered solvent molecules and anions. It seems not a serious problem because the number of the problematic reflections is ignorable compared to that of the reflections used in the refinement (> 50000).

“PLAT973_ALERT_2_A Check Calcd Positive Resid. Density on Pd3 5.20 eA⁻³”

These alerts are probably derived from some inefficiency in the absorption correction. The occupation of Pd atoms at these sites is obvious from the chemical information and processes.

“PLAT084_ALERT_3_B High wR2 Value (i.e. > 0.25) 0.36 Report”

This alert was presumably derived from the poorly modeled diffractions for unsolved anions and solvent molecules.

“PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?) O2I Check”

The hydrogen atoms could not be located on the water molecules.

“PLAT430_ALERT_2_B Short Inter D...A Contact O1A ..O59 . 2.67 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT975_ALERT_2_B Check Calcd Resid. Dens. 1.05A From O126 1.75 eA⁻³”
There might be highly disordered solvent molecules.

1a•(2c)₂ (ks27_2)

“PLAT201_ALERT_2_A Isotropic non-H Atoms in Main Residue(s)33 Report”

These alerts were derived from solvent molecules/anions and TMEDA ligands of the cages, which were highly disordered. These parts were refined isotropically.

“PLAT430_ALERT_2_A Short Inter D...A Contact O1F ..O3F . 1.97 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT602_ALERT_2_A VERY LARGE Solvent Accessible VOID(S) in Structure ! Info”

The crystal has large voids filled with severely disordered anions, water molecules and possibly disordered guest molecules with low occupancy. SQUEEZE procedure was used to deal with such molecules.

“PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 71 Check”

This alert was derived from low quality of data, possibly due to the saturated reflections or poorly modeled disordered solvent molecules and anions. It seems not a serious problem because the number of the problematic reflections is ignorable compared to that of the reflections used in the refinement (> 100000).

“PLAT973_ALERT_2_A Check Calcd Positive Resid. Density on Pd01 3.78 eA⁻³”

These alerts are probably derived from some inefficiency in the absorption correction. The occupation of Pd atoms at these sites is obvious from the chemical information and processes.

“PLAT084_ALERT_3_B High wR2 Value (i.e. > 0.25) 0.36 Report”

This alert was derived from poorly modeled disordered solvent molecules and anions and low quality of data.

“PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of C4A1 Check”

These alerts were derived from TMEDA ligands of the cages, which were highly disordered.

“PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?) O65 Check”

The hydrogen atoms could not be located on the water molecules.

“PLAT430_ALERT_2_B Short Inter D...A Contact O1C ..O44 . 2.67 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT939_ALERT_3_B Large Value of Not (SHELXL) Weight Optimized S . 156.12 Check”

This alert was derived from low quality of data.

“PLAT971_ALERT_2_B Check Calcd Resid. Dens. 0.22A From Pd08 3.27 eA⁻³”

There should be a disordered Pd atom, but that was not assigned because of the very low ratio of the minor disorder.

“PLAT975_ALERT_2_B Check Calcd Resid. Dens. 0.48A From O3E 1.68 eA⁻³”

There might be highly disordered solvent molecules.

1a•2d (ks50-2_2)

“PLAT201_ALERT_2_A Isotropic non-H Atoms in Main Residue(s)21 Report”

Some of water molecules, anions, TMEDA ligands of the cages and guest molecules outside the cavity were refined isotropically due to severe disorder.

“PLAT430_ALERT_2_A Short Inter D...A Contact O3J ..O86 . 2.51 Ang.”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT602_ALERT_2_A VERY LARGE Solvent Accessible VOID(S) in Structure ! Info”

The crystal has large voids filled with severely disordered anions, water molecules and possibly disordered guest molecules with low occupancy. SQUEEZE procedure was used to deal with such molecules.

“PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 60 Check”

This alert was derived from low quality of data, possibly due to the saturated reflections or poorly modeled disordered solvent molecules and anions. It seems not a serious problem because the number of the problematic reflections is ignorable compared to that of the reflections used in the refinement (> 70000).

“PLAT971_ALERT_2_A Check Calcd Resid. Dens. 0.30A From Pd4 3.85 eA⁻³”

There should be a disordered Pd atom, but that was not assigned because of the very low ratio of the minor disorder.

“PLAT220_ALERT_2_B Non-Solvent Resd 1 C Ueq(max)/Ueq(min) Range 7.8 Ratio”

These alerts were derived from TMEDA ligands of the cages, which were highly disordered.

“PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of C5W Check”

This alert is derived from a guest molecule outside the cage cavity. This molecule is highly disordered and could not be fully assigned.

“PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C6W Check”

This alert is derived from a guest molecule outside the cage cavity. This molecule is highly disordered and could not be fully assigned.

“PLAT260_ALERT_2_B Large Average Ueq of Residue Including O40 0.355 Check”

These alerts were derived from solvent molecules/anions, which were highly disordered.

“PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?) O59 Check”

The hydrogen atoms could not be located on the water molecules.

“PLAT430_ALERT_2_B Short Inter D...A Contact O1 ..O1J . 2.67 Ang. Check”

These alerts were derived from the modeled atoms of nitrate anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT975_ALERT_2_B Check Calcd Resid. Dens. 0.80A From O17 1.90 eA⁻³”

There might be highly disordered solvent molecules.

“PLAT975_ALERT_2_B Check Calcd Resid. Dens. 0.72A From O02C 1.72 eA⁻³”

There might be highly disordered solvent molecules.

1a•(2e)₂•S1 (ht1350b_2)

“PLAT430_ALERT_2_A Short Inter D...A Contact O1' ..O13 2.51 Ang. Check”

These alerts were derived from the modeled atoms of counter anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 18 Check”

This alert was derived from low quality of data, possibly due to the saturated reflections or poorly modeled disordered solvent molecules and anions. It seems not a serious problem because the number of the problematic reflections is ignorable compared to that of the reflections used in the refinement (> 40000).

“PLAT084_ALERT_3_B High wR2 Value (i.e. > 0.25) 0.38 Report”

This alert was derived from poorly modeled disordered solvent molecules and anions and low quality of data.

“PLAT214_ALERT_2_B Atom O5Y (Anion/Solvent) ADP max/min Ratio 5.5 prolat”

This alert was derived from the modeled atom of the co-crystallized sulfonate anion. A part of the anion was highly disordered.

“PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors of C9Y Check”

These alerts were mainly derived from co-crystallized anions, which were highly disordered.

“PLAT260_ALERT_2_B Large Average Ueq of Residue Including O10Y 0.306 Check”

These alerts were mainly derived from co-crystallized anions and solvent molecules, which were highly disordered.

“PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing ?) O1 Check”

The hydrogen atoms could not be located on the water molecules.

“PLAT430_ALERT_2_B Short Inter D...A Contact O1 ..O4AC 2.77 Ang. Check”

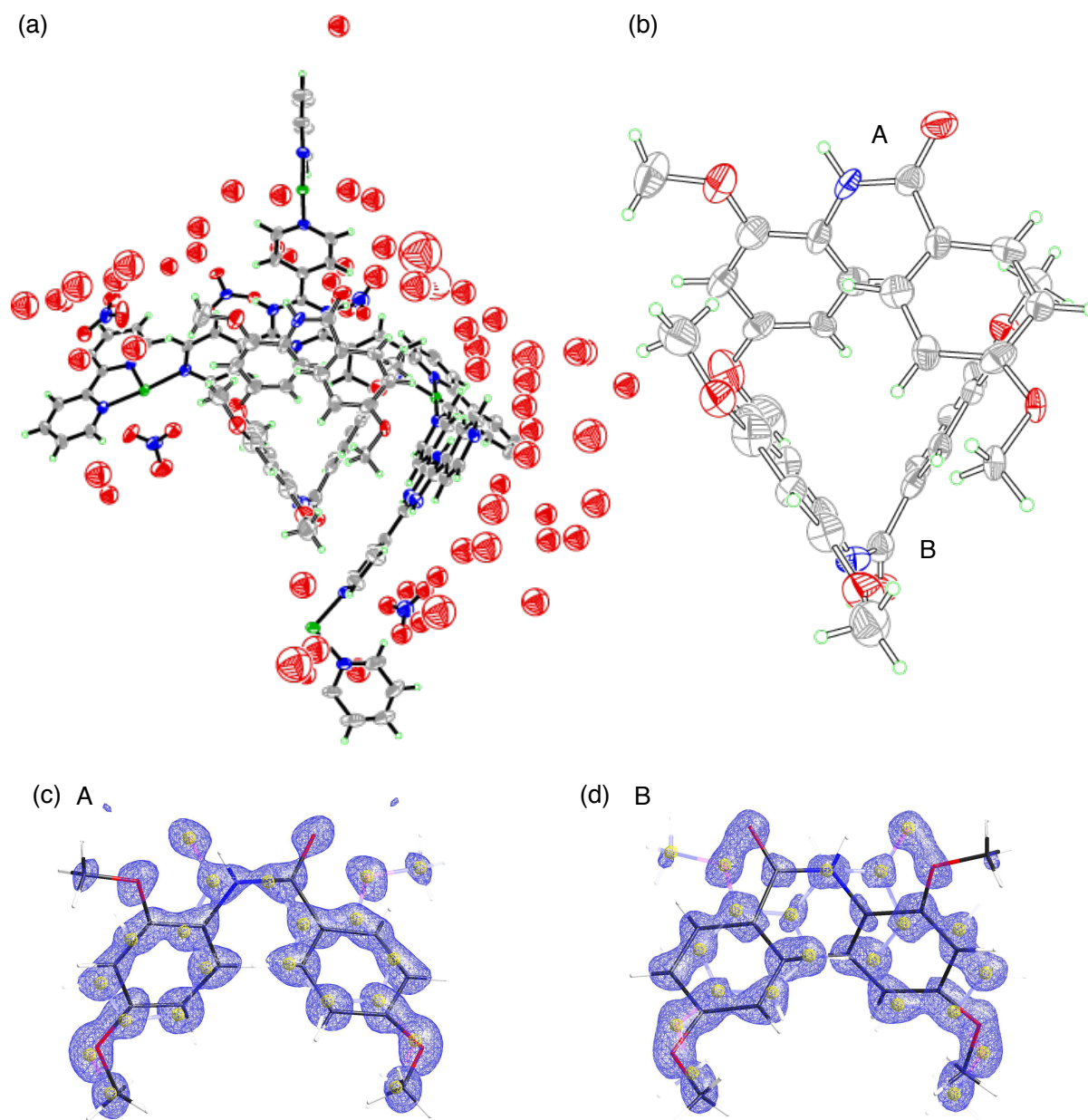
These alerts were derived from the modeled atoms of counter anions or solvent water molecules with full or partial occupancies. Some of them are highly disordered and therefore the precise positions cannot be determined.

“PLAT973_ALERT_2_B Check Calcd Positive Resid. Density on Pd3A 1.59 eA⁻³”

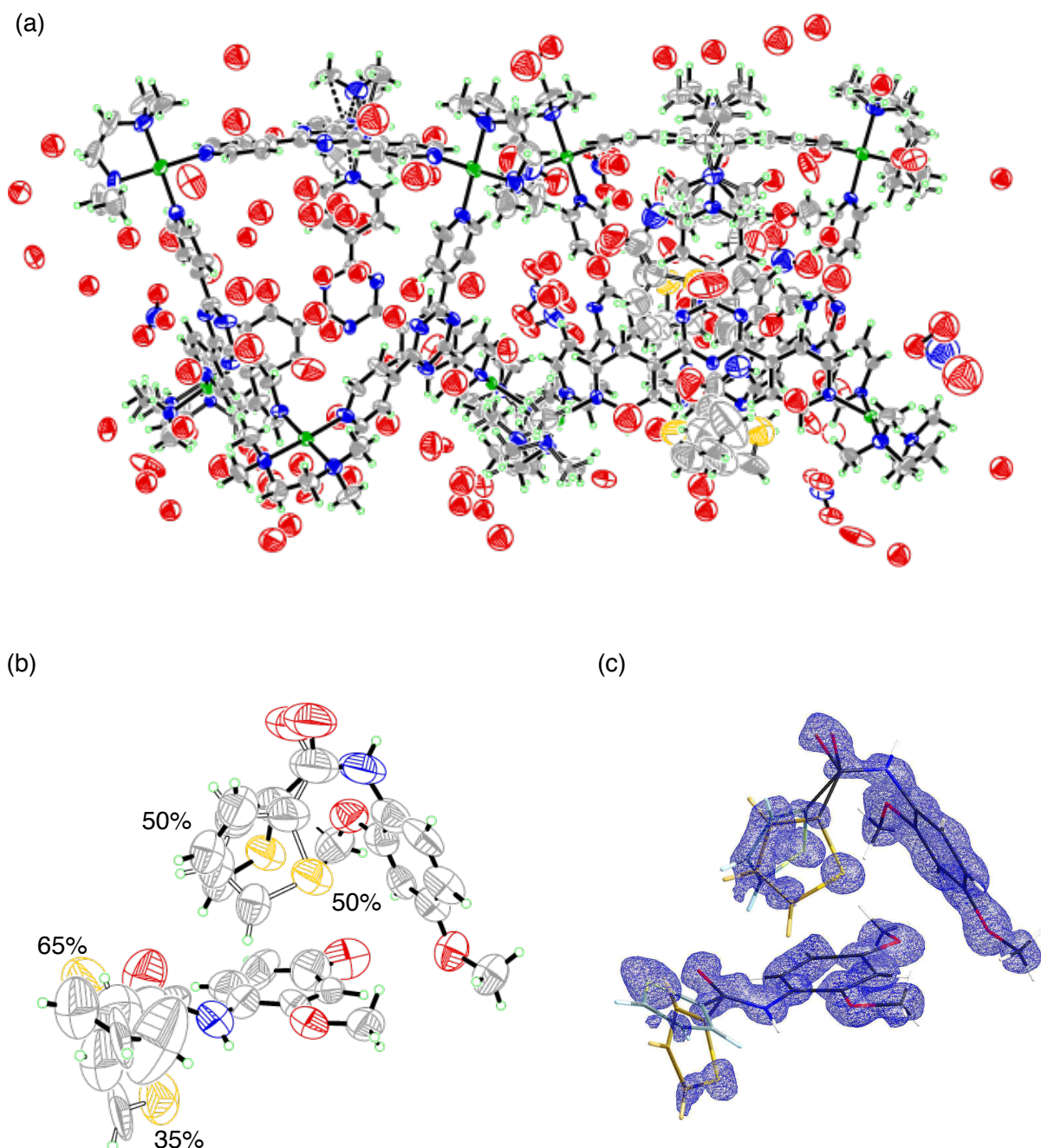
These alerts are probably derived from some inefficiency in the absorption correction. The occupation of Pd atoms at these sites is obvious from the chemical information and processes.

“PLAT975_ALERT_2_B Check Calcd Resid. Dens. 0.64A From O5Z 1.69 eA⁻³”

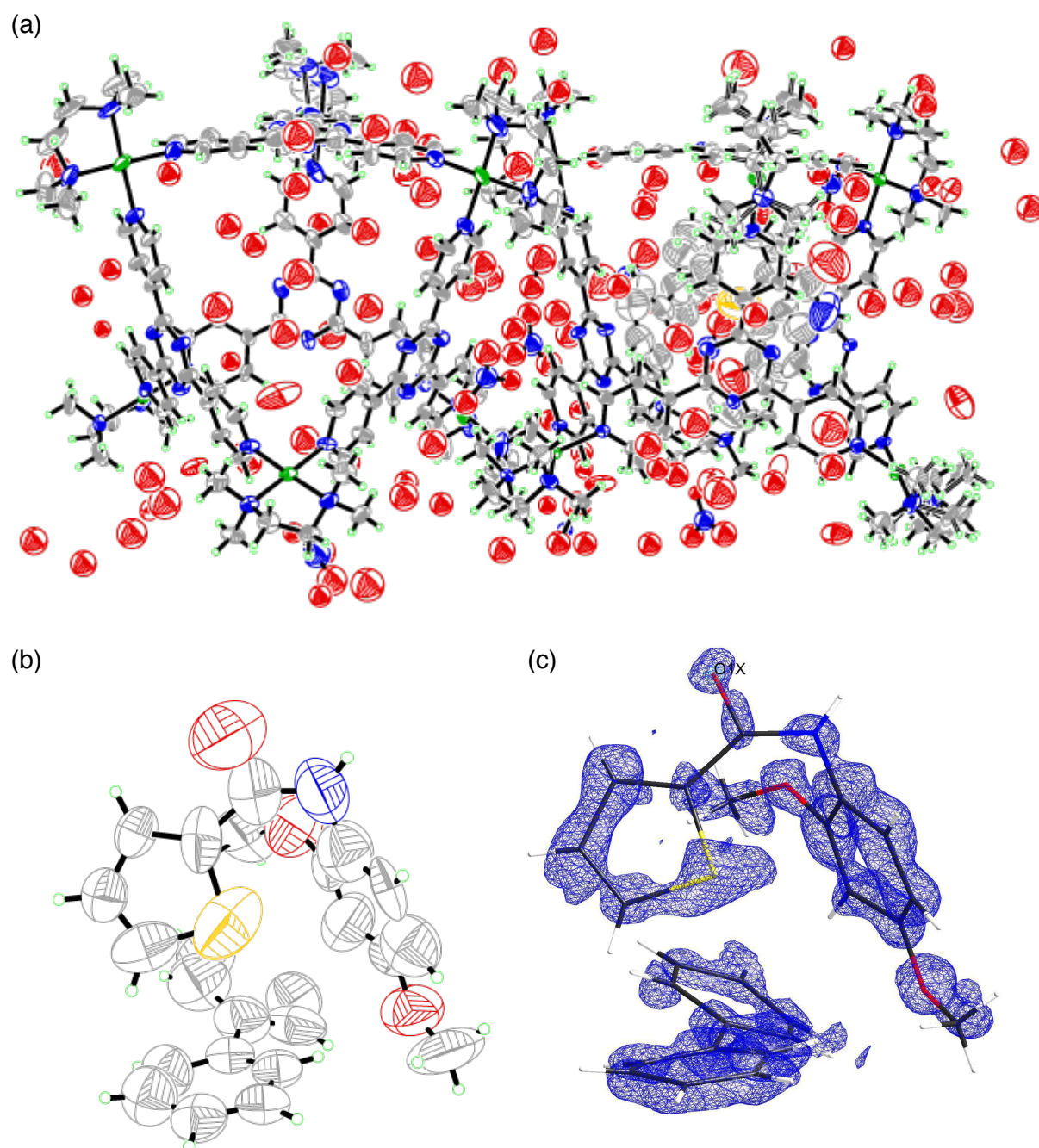
There might be highly disordered solvent molecules.



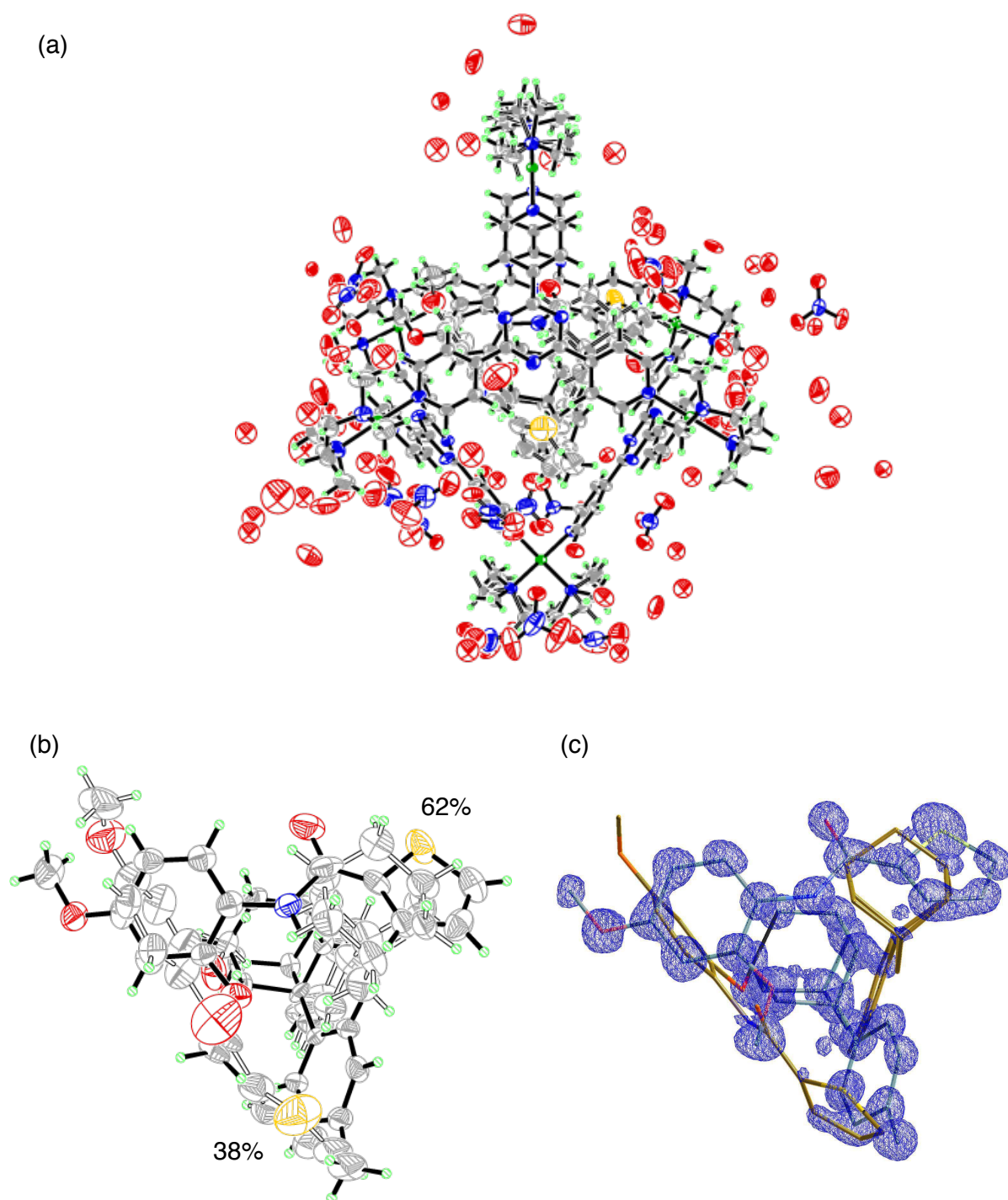
Supplementary Figure 37. Crystal structures of **1b•(2a)₂** (CCDC reference number 1949143). ORTEP drawings (30% probability ellipsoids) of (a) a refinement structure and (b) the included guests in **1b•(2a)₂**. (c), (d) F_o maps around the guest molecules ($2.0 \text{ e} \cdot \text{\AA}^{-3}$, $\sigma = 1.4$). The disordered guests generated around the crystallographic C_2 axis are highlighted in yellow.



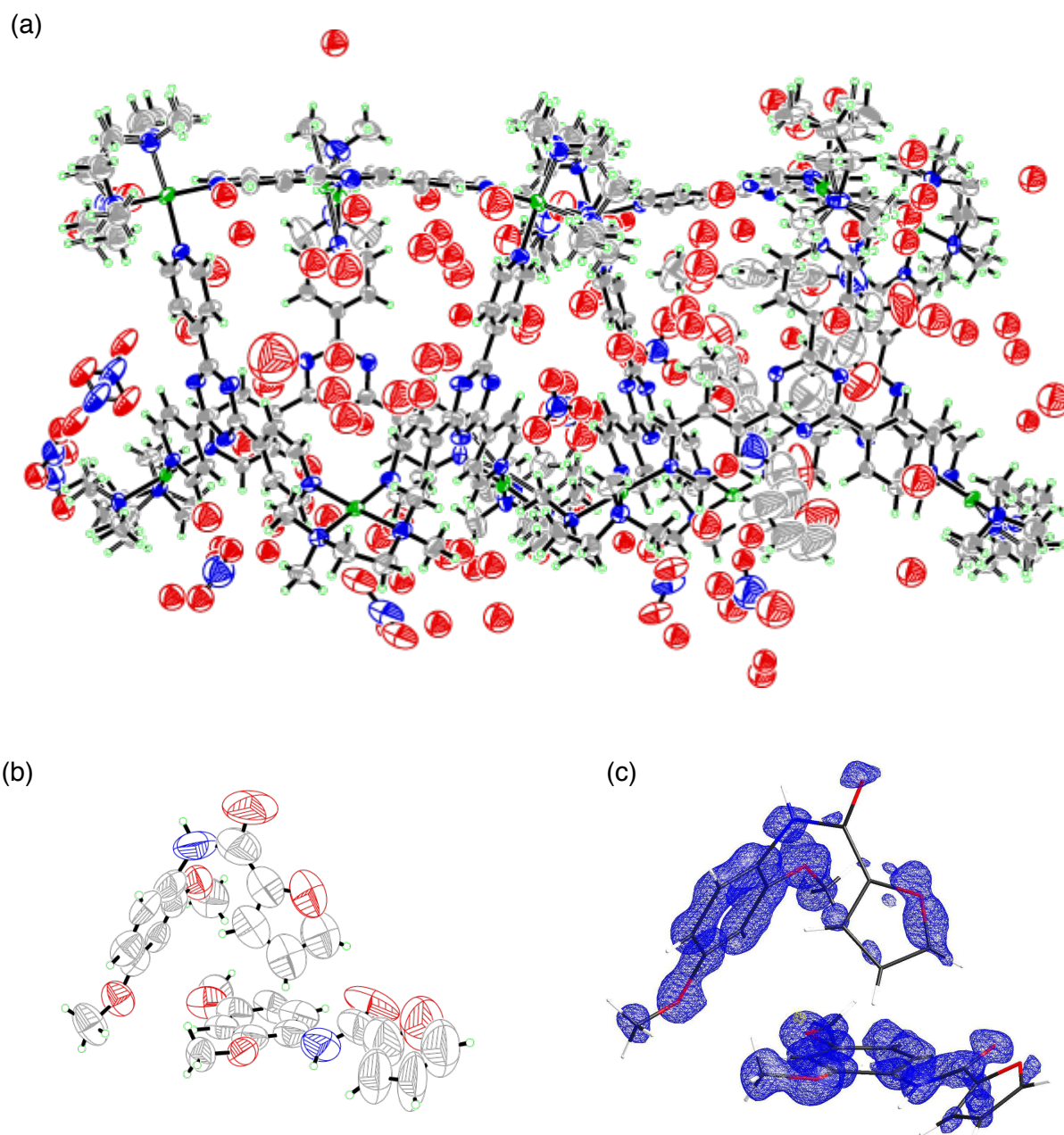
Supplementary Figure 38. Crystal structures of **1a•(2b)₂** (CCDC reference number 1949144). ORTEP drawings (30% probability ellipsoids) of (a) a refinement structure and (b) the included guests in **1a•(2b)₂** (occupancies of the disordered guest molecules are shown in the figure). (c) F_o maps around the guest molecules ($0.78 \text{ e} \cdot \text{\AA}^{-3}$, $\sigma = 0.65$). Electron density possibly from disordered guest molecules is also observed in the second cage. However, attempt for the structure refinement failed.



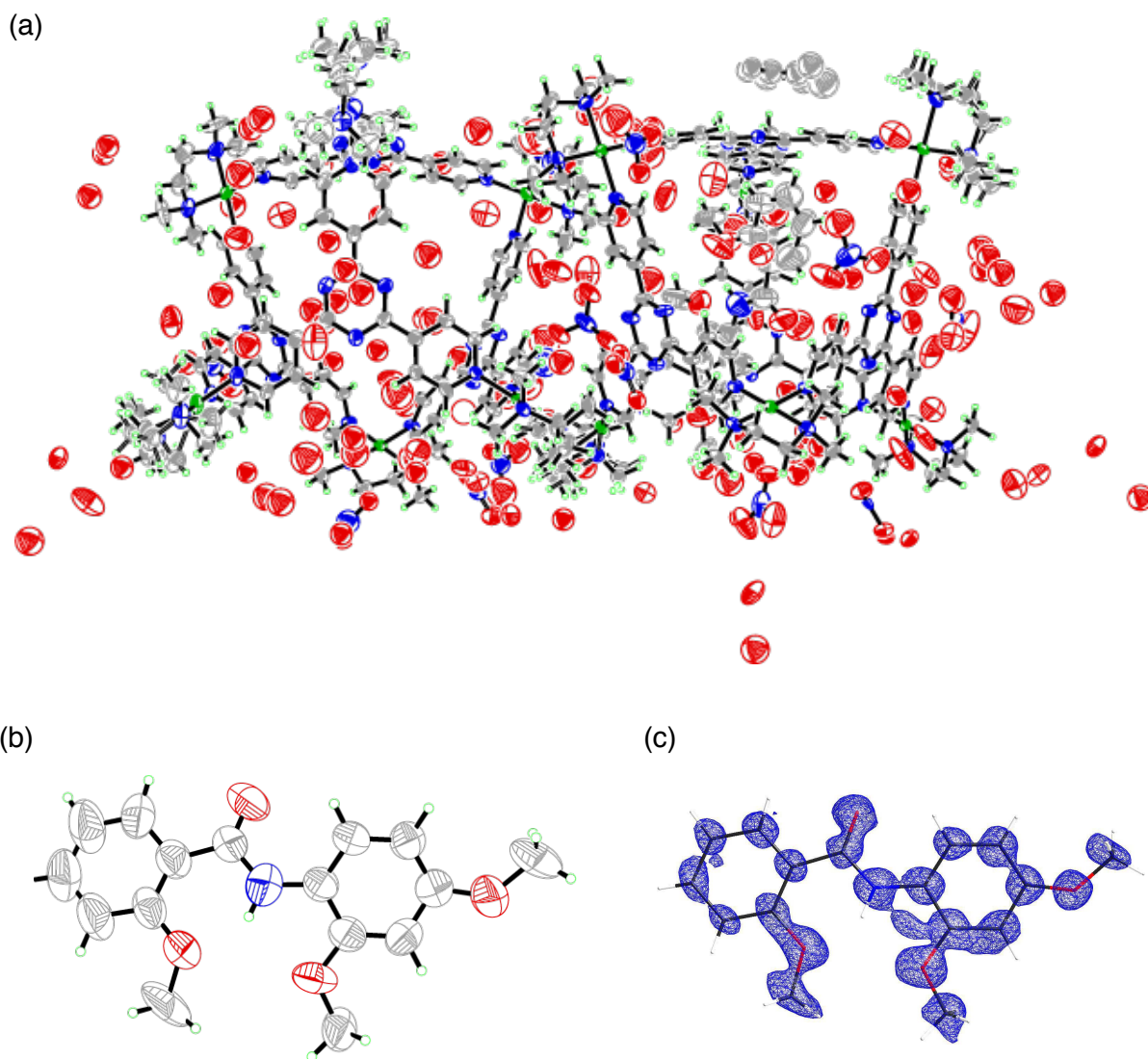
Supplementary Figure 39. Crystal structures of **1a•(2b•3a)** (CCDC reference number 1949145). ORTEP drawings (30% probability ellipsoids) of (a) a refinement structure and (b) the included guests in **1a•(2b•3a)**. (c) F_o maps around the guest molecules ($0.81 \text{ e} \cdot \text{\AA}^{-3}$, $\sigma = 0.67$).



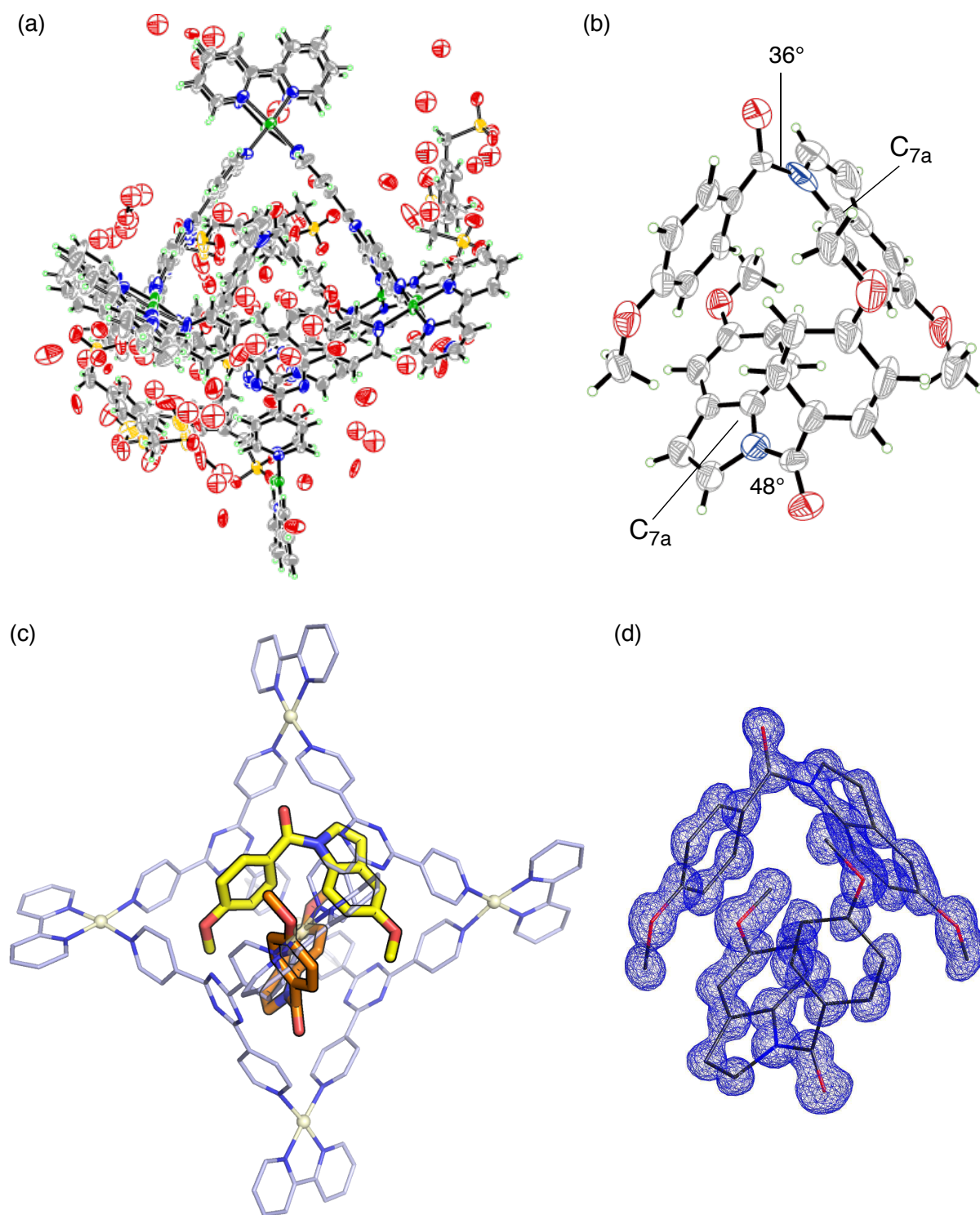
Supplementary Figure 40. Crystal structures of **1a•(2b•4)** (CCDC reference number 1949146). ORTEP drawings (30% probability ellipsoids) of (a) a refinement structure and (b) the included guests in **1a•(2b•4)** (occupancies of the disordered guest molecules are shown in the figure). (c) F_o maps around the guest molecules ($0.97 \text{ e} \cdot \text{\AA}^{-3}$, $\sigma = 0.81$).



Supplementary Figure 41. Crystal structures of **1a•(2c)₂** (CCDC reference number 1949149). ORTEP drawings (30% probability ellipsoids) of (a) a refinement structure and (b) the included guests in **1a•(2c)₂**. (c) F_o maps around the guest molecules ($0.84 \text{ e} \cdot \text{\AA}^{-3}$, $\sigma = 0.70$). Electron density possibly from disordered guest molecules is also observed in the second cage. However, attempt for the structure refinement failed.



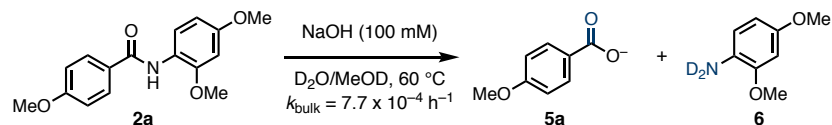
Supplementary Figure 42. Crystal structures of **1a•2d** (CCDC reference number 1949150). ORTEP drawings (30% probability ellipsoids) of (a) a refinement structure and (b) the included guests in **1a•2d**. (c) F_o maps around the guest molecules ($0.87 \text{ e} \cdot \text{\AA}^{-3}$, $\sigma = 0.72$).



Supplementary Figure 43. Crystal structures of **1a•(2e)₂•S1** (CCDC reference number 1949151). ORTEP drawings (30% probability ellipsoids) of (a) a refinement structure and (b) the included guests in **1a•(2e)₂**. The dihedral angles ($C_{7a}-N-C(O)-C$, ω) of the guests are shown in the figure. (c) The guest orientation in the structure. (d) F_o maps around the guest molecules ($1.0 \text{ e} \cdot \text{\AA}^{-3}$, $\sigma = 0.61$).

6. Hydrolysis of amides under basic conditions

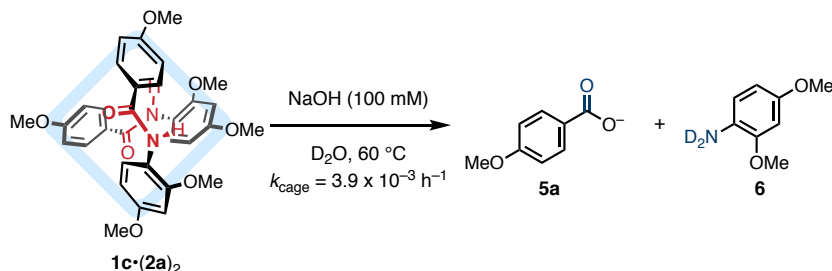
Reaction of **2a** in a bulk solution under basic conditions



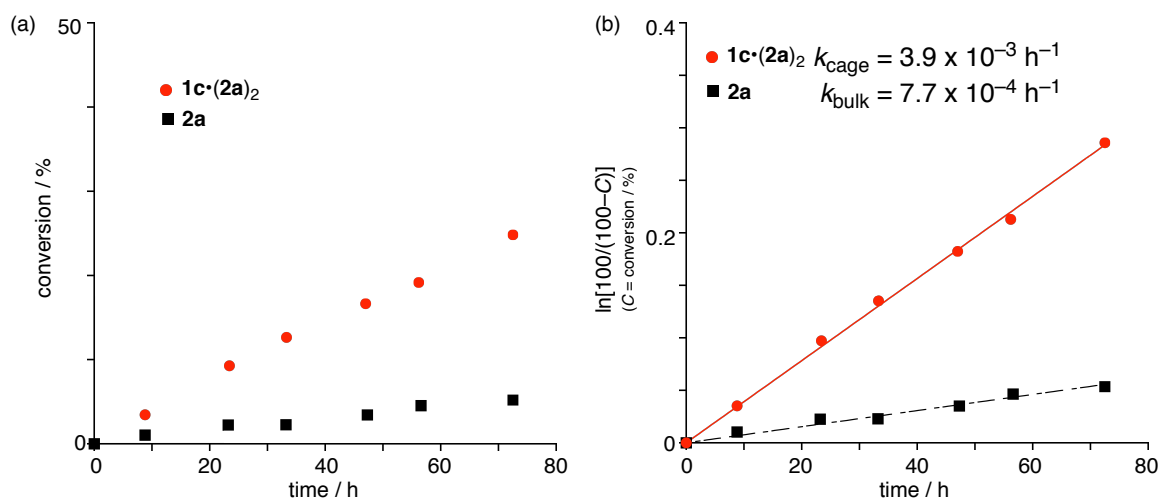
500 mM NaOH in D_2O (0.25 mL) was added to a solution of **2a** (0.57 mg, 2 μmol) in $D_2O/MeOD$ (3:5, 1.0 mL) and stirred at $60\text{ }^{\circ}C$ for 3 d. Conversions were monitored every 0.5 d for 3 d by 1H NMR analysis of the extract based on the ratio between **2a** and **6**. The reaction constant k_{bulk} was determined from averaged conversions of three trials as $7.7 \times 10^{-4} \text{ h}^{-1}$ by a curve-fitting method with the following first-order kinetic equation.

$$\ln\left(\frac{100}{100 - C}\right) = kt \quad C : \text{conversion} [\%]$$

Reaction of **2a** with cage **1c** under basic conditions

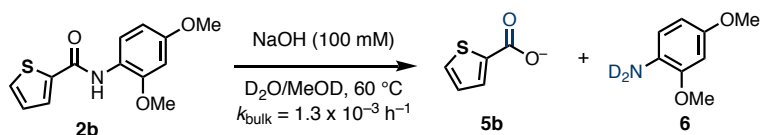


500 mM NaOH in D_2O (0.25 mL) was added to an aqueous solution of **1c·(2a)₂** (**1c** = 3 mM, 1.0 mL, 3 μmol) and stirred at $60\text{ }^{\circ}C$. Conversions were monitored every 0.5 d for 3 d after extraction with $CDCl_3$ by 1H NMR analysis of the extract based on the ratio between **2a** and **6**. The rate constant k_{cage} was determined from averaged conversions of three trials as $3.9 \times 10^{-3} \text{ h}^{-1}$ ($k_{\text{cage}}/k_{\text{bulk}} = 5.1$) by the curve-fitting method with the first-order kinetic equation.



Supplementary Figure 44. (a) Time-conversion plots for the hydrolysis of **2a** with (red circle) /without (black square) cage **1c** under basic conditions. (b) Curve-fitting with the first-order kinetic equation for the hydrolysis of **2a**.

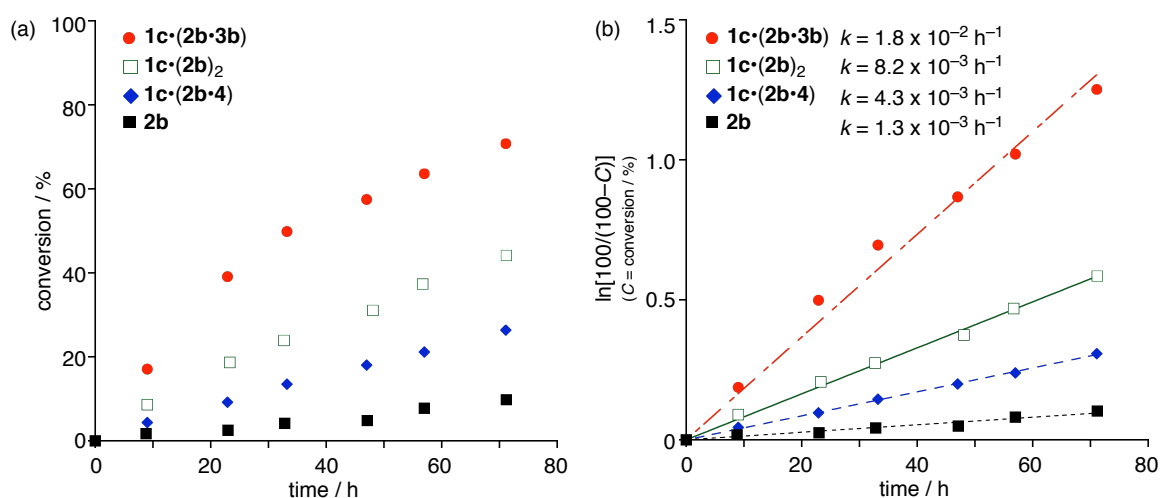
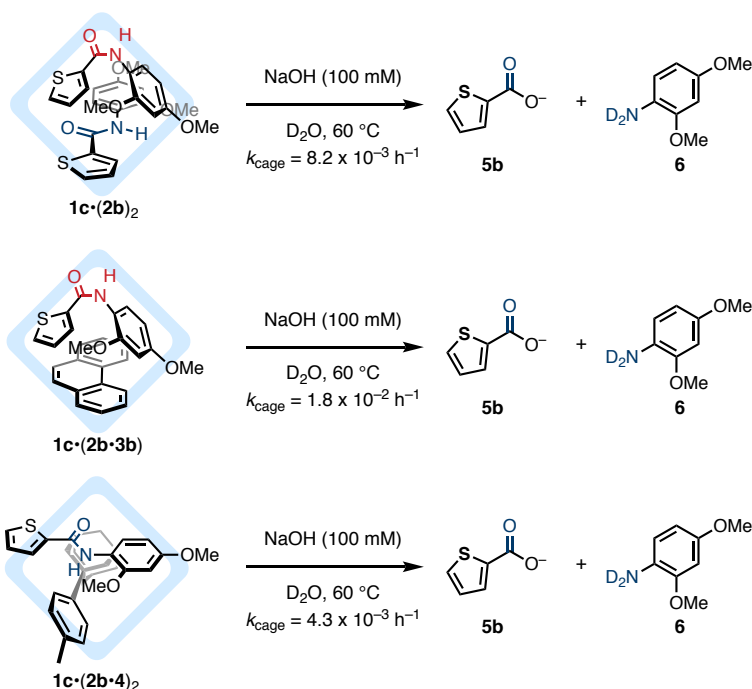
Reaction of 2b without cage 1c under basic conditions



A solution of **2b** (0.59 mg, 2 μmol) instead of **2a** was used in the reaction of **2b**. The reaction constant k_{bulk} was determined as $1.3 \times 10^{-3} \text{ h}^{-1}$.

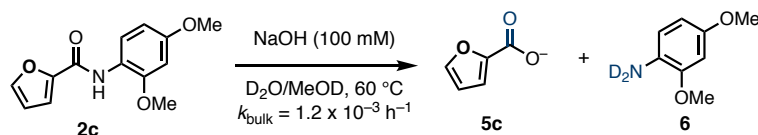
Reaction of 2b with cage 1c under basic conditions

An aqueous solution of **1c**•(**2b**)₂, **1c**•(**2b**•**3b**) and **1c**•(**2b**•**4**) [**1c**] = 3 mM, 1.0 mL, 3 μmol) instead of **1c**•(**2a**)₂ were used in the reaction of **2b**. The reaction constant k_{cage} were determined as $8.2 \times 10^{-3} \text{ h}^{-1}$ ($k_{\text{cage}}/k_{\text{bulk}} = 6.1$), $1.8 \times 10^{-2} \text{ h}^{-1}$ ($k_{\text{cage}}/k_{\text{bulk}} = 14$) and $4.3 \times 10^{-3} \text{ h}^{-1}$ ($k_{\text{cage}}/k_{\text{bulk}} = 3.2$), respectively.



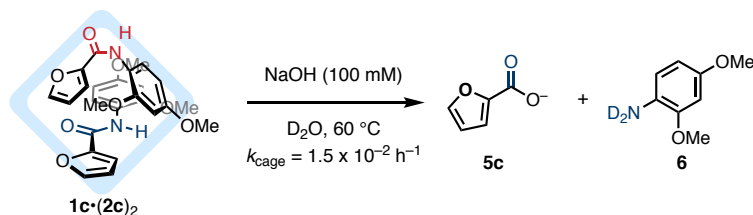
Supplementary Figure 45. (a) Time-conversion plots for the hydrolysis of **1c**•(**2b**•**3b**) (red circle), **1c**•(**2b**)₂ (green square), **1c**•(**2b**•**4**) (blue lozenge) and **2b** (black square) under basic conditions. (b) Curve-fitting with the first-order kinetic equation for the hydrolysis of **2b**.

Reaction of **2c** without cage **1c** under basic conditions

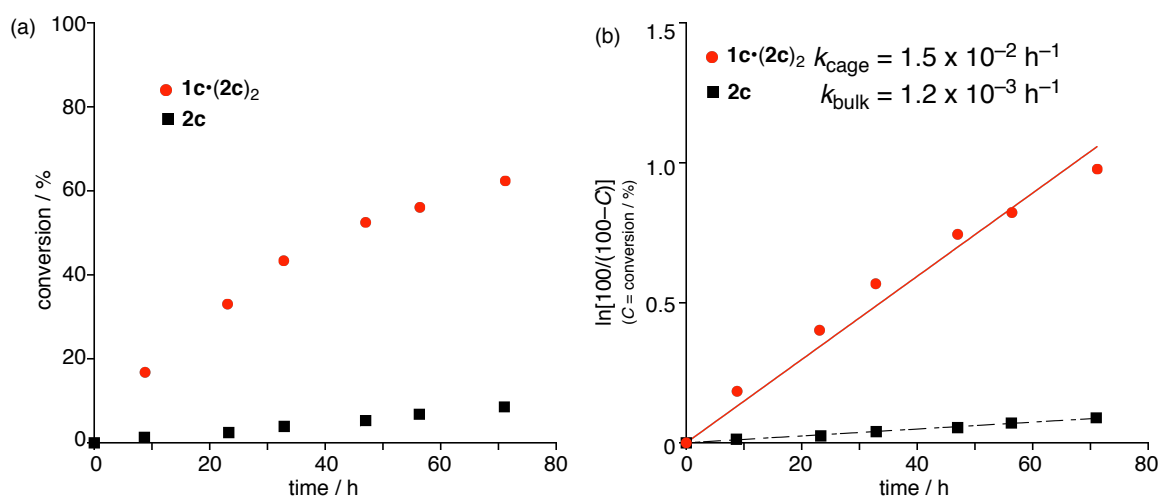


A solution of **2c** (0.62 mg, 2 μmol) instead of **2a** was used in the reaction of **2c**. The reaction constant k_{bulk} was determined as $1.2 \times 10^{-3} \text{ h}^{-1}$.

Reaction of **2c** with cage **1c** under basic conditions

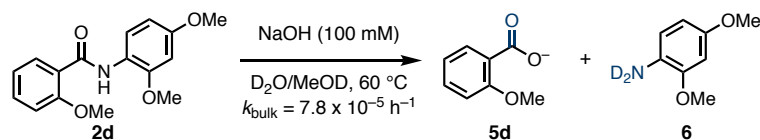


An aqueous solution of **1c**·(**2c**)₂ ([**1c**] = 3 mM, 1.0 mL, 3 μmol) instead of **1c**·(**2a**)₂ was used in the reaction of **2c**. The reaction constant k_{cage} was determined as $1.5 \times 10^{-2} \text{ h}^{-1}$ ($k_{\text{cage}}/k_{\text{bulk}} = 12$).



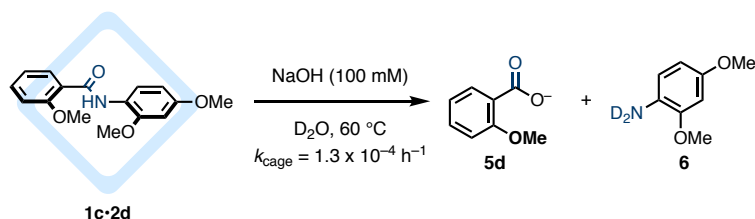
Supplementary Figure 46. (a) Time-conversion plots for the hydrolysis of **2c** with (red circle) /without (black square) cage **1c** under basic conditions. (b) Curve-fitting with the first-order kinetic equation for the hydrolysis of **2c**.

Reaction of **2d** without cage **1c** under basic conditions

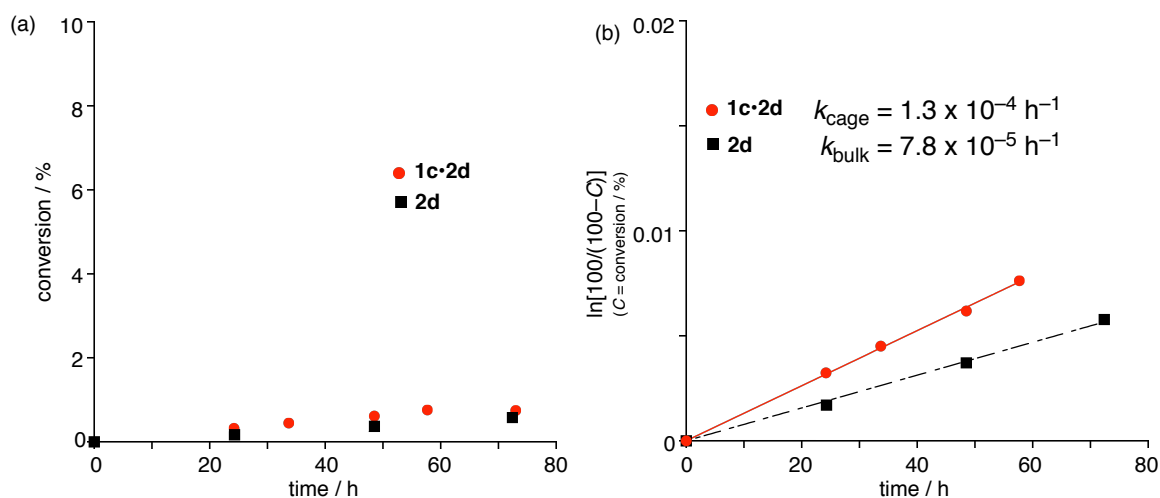


A solution of **2d** (0.65 mg, 2 μmol) instead of **2a** was used in the reaction of **2d**. The reaction constant k_{bulk} was determined as $7.8 \times 10^{-5} \text{ h}^{-1}$.

Reaction of **2d** with cage **1c** under basic conditions

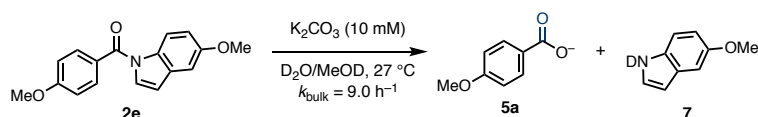


An aqueous solution of **1c·2d** ($[\mathbf{1c}] = 3 \text{ mM}$, 1.0 mL, 3 μmol) instead of **1c·(2a)₂** was used in the reaction of **2d**. The reaction constant k_{cage} was determined as $1.3 \times 10^{-4} \text{ h}^{-1}$ ($k_{\text{cage}}/k_{\text{bulk}} = 1.7$).



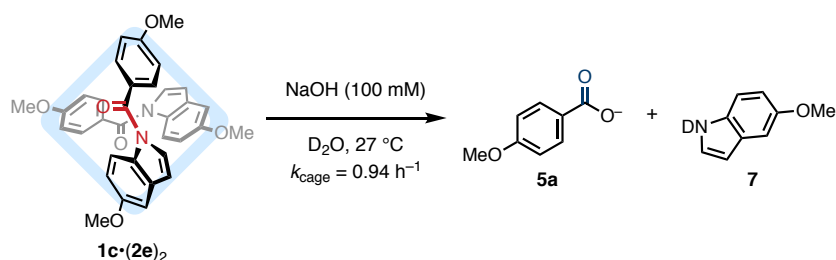
Supplementary Figure 47. (a) Time-conversion plots for the hydrolysis of **2d** with (red circle) /without (black square) cage **1c** under basic conditions. (b) Curve-fitting with the first-order kinetic equation for the hydrolysis of **2d**.

Reaction of 2e without cage 1c under basic conditions

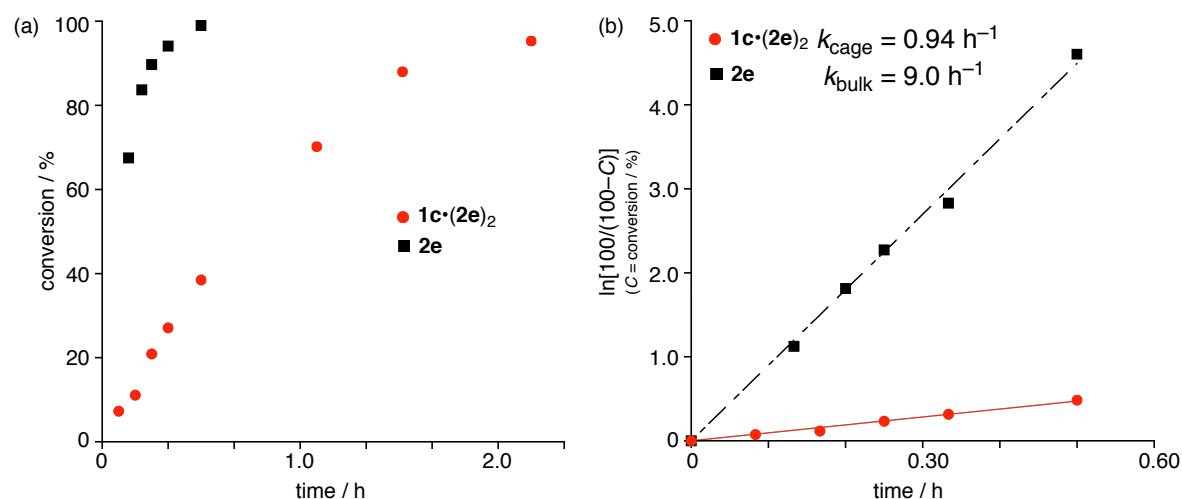


A D_2O solution of K_2CO_3 (20 mM, 1.0 mL) was added to a CD_3OD solution of **2e** (0.38 mg, 0.68 μ mol, 1.0 mL) and stirred at $27^\circ C$. Conversions were monitored by 1H NMR measurements of the reaction mixture. The reaction constant k_{bulk} was determined as $9.0\ h^{-1}$.

Reaction of 2e with cage 1c under basic conditions



A D_2O solution of K_2CO_3 (20 mM, 0.50 mL) was added to a D_2O solution of **1c•(2e)₂** (**1c** = 2.0 mM, 0.50 mL) and stirred at $27^\circ C$. Conversions were monitored by 1H NMR measurements after extraction of the reaction mixture with $CDCl_3$. The reaction constant k_{cage} was determined as $0.94\ h^{-1}$ ($k_{cage}/k_{bulk} = 0.11$).



Supplementary Figure 48. (a) Time-conversion plots for the hydrolysis of **2e** with (red circle) /without (black square) cage **1c** under basic conditions. (b) Curve-fitting with the first-order kinetic equation for the hydrolysis of **2e**.

[References]

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