Supporting Information

Confinement of Water-Soluble Cationic Substrates in a Cationic Molecular Cage by Capping the Portals with Tripodal Anions

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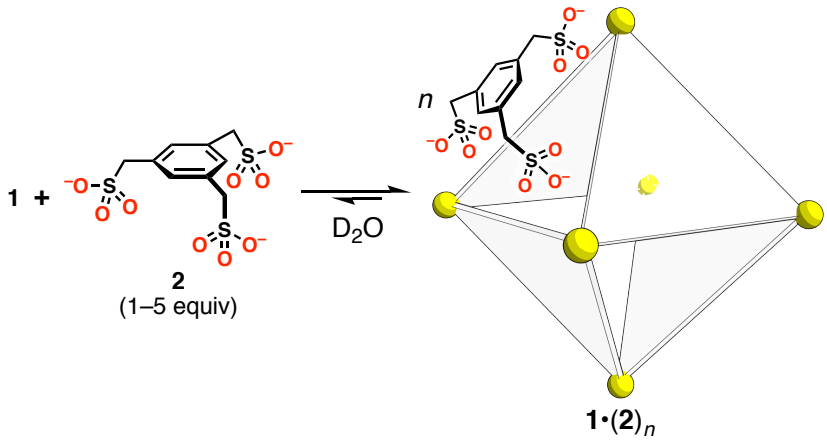
1. Materials and instrumentations

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer equipped with a CP-TCI cryoprobe or a Bruker AVANCE III HD 500 MHz spectrometer equipped with a PABBO probe (500 MHz for ^{1}H NMR and 125MHz for ^{13}C NMR) at 300K unless otherwise stated. TMS ($CDCl_3$ solution) in a capillary served as an internal standard (δ = 0 ppm for ^{1}H and ^{13}C NMR) for D_2O solutions. Solvents and reagents were purchased from TCI Co., Ltd., FUJIFILM Wako Pure Chemical Corp., Sigma-Aldrich Co., and Kanto Chemical Co., Inc. and used without further purification. Coordination cage **1**[1] and Sodium 1,3,5-benzenetrimethanesulfonate (**2**)[2] were prepared according to the established methods.

Single crystal X-ray diffraction data were collected on a BRUKER APEX-II CCD rotating anode diffractometer equipped with focusing mirrors with Mo*K*α (λ = 0.71073 Å) radiation under cryogenic conditions, which are controlled with a cryostat system equipped with a N_2 generator (Japan Thermal Eng. Co., Ltd.). Bruker APEX2 software was used for the data collections and the data processing. The structures were solved by SHELXS-97 package using direct methods and refined by full-matrix least-squares methods using SHELXL-2017/1 embedded in ShelXle suits.[3,4] All C-H and N-H hydrogen positions were calculated and refined using a riding atom model after the refinement of the non-hydrogen atoms. In all structures, the framework atoms of **1** were firstly located and refined and then the atoms of anion **2**, guests and other counter anions were located and refined. The large Q-peaks isolated from other atoms were assigned as water oxygen atoms and refined. Careful refinements with minimal restraints around the disordered parts of anion **2** and capping ligands of **1** clearly revealed the multiple interactions between cage **1**, anion **2** and **3**. For the structure of **1**·**2**, the SQUEEZE program in PLATON[5] was used for the analysis to remove the disordered unassignable solvent densities in the void. Although several alerts A and B are raised in the CheckCIF, these alerts are caused by the disordered water molecules in the crystal and therefore do not raise serious concerns for the discussions. The responses for these alerts have been described in the CIF files.

2. Addition of tripodal anion 2 to cage 1



A typical procedure

Tripodal anion **2** (0.60 mg, 1.4 μmol, 1.1 equiv) was added to a D_2O solution of cage **1** (1.67 mM, 0.75 mL, 1 equiv) and stirred at room temperature for 1 h. Then ^{1}H NMR spectrum of the solution was measured. As for the 1:5 mixture of **1** and **2**, the D_2O solution of cage **1** was diluted to 1.25 mM to avoid the precipitation.

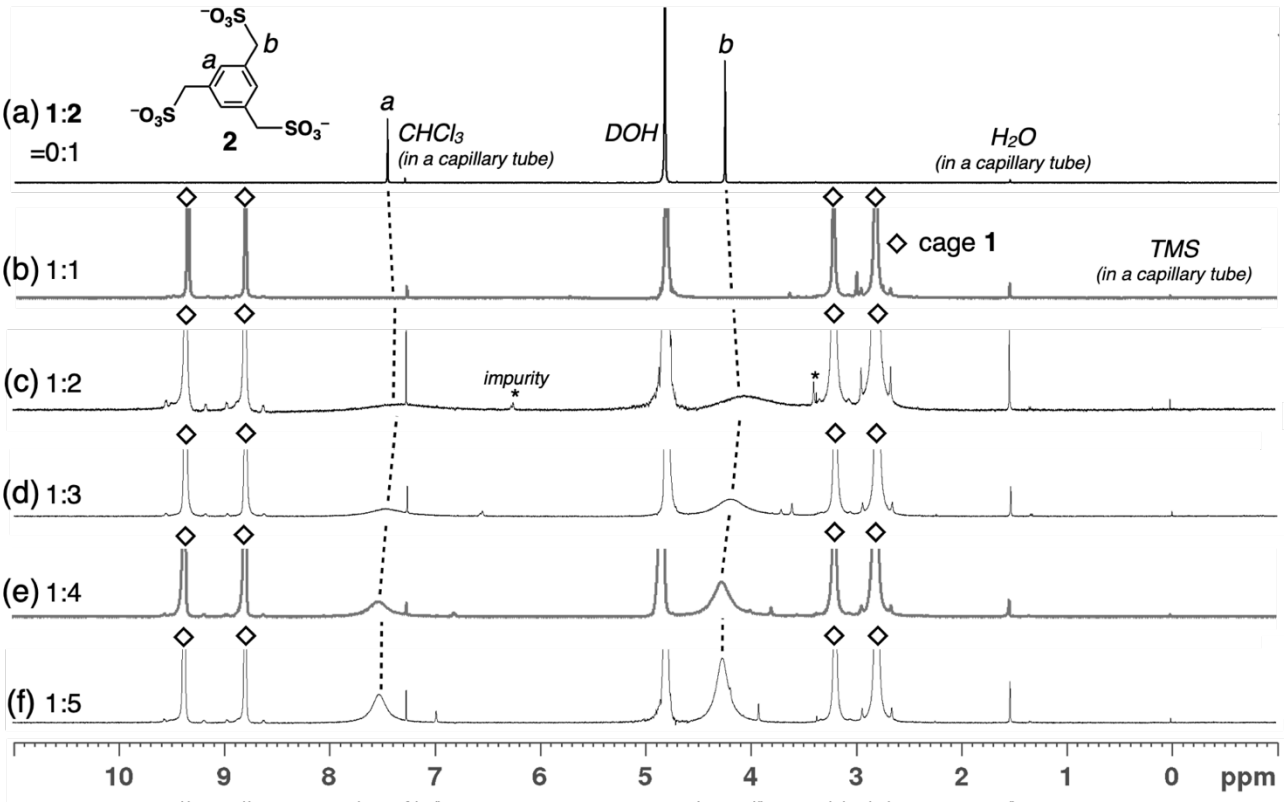


Figure S1. ^{1}H NMR spectra (500 MHz, D_2O, 300 K) of (a) anion **2** and (b)–(f) 1:*n* mixture of **1** and **2**.

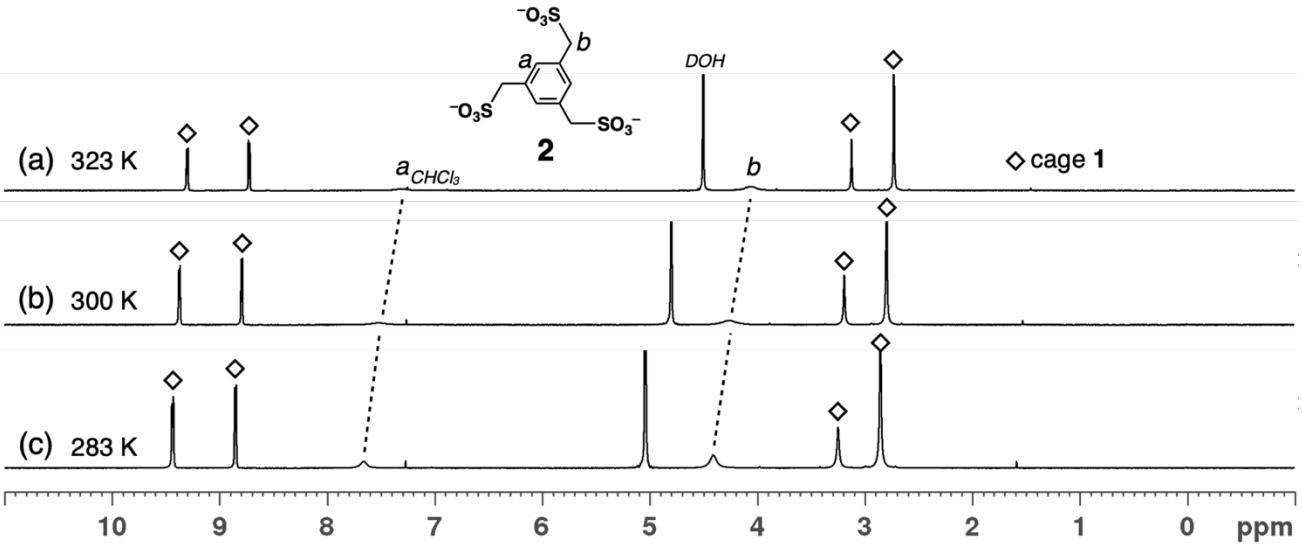


Figure S2. ^{1}H NMR spectra (500 MHz, D_2O) of 1:4 mixture of **1** and **2** at (a) 323 K, (b) 300 K, and (c) 283 K.

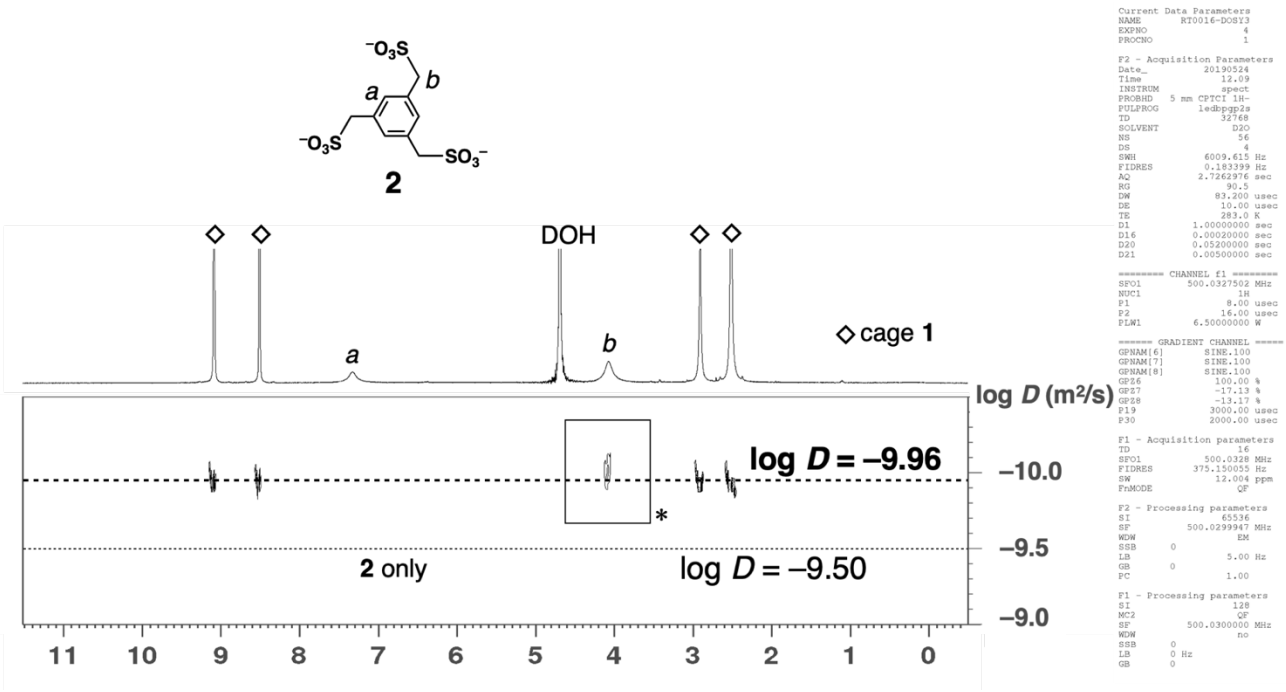


Figure S3. ^{1}H DOSY NMR spectrum (500 MHz, D_2O, 283 K) of 1:4 mixture of **1** and **2**. The signal of anion **2** denoted by an asterisk is shown in the one-tenth threshold level (diffusion time: 52 ms, length of diffusion gradient: 2 ms, number of increments: 16, number of scans: 56, processing method: exponential).

3. X-ray crystallographic analyses of 1·2

Procedure for crystallization

The reaction mixture of **1·2** was stood at 50 ºC and the water solvent was allowed to evaporate. After two weeks, a single crystal suitable for X-ray diffraction analysis was obtained.

Crystal data for 1·2

Table S1. Crystal data and structure refinement for 1·2

Identification code	ima2_a_sq	
CCDC number	2022050	
Empirical formula	$C_{117}H_{153}N_{38}O_{77.67}Pd_6S_3$	
Formula weight	4069.01	
Temperature	90(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*I*ma2	
Unit cell dimensions	a = 32.464(3) Å	α = 90°
	b = 40.003(4) Å	β = 90°
	c = 18.7989(16) Å	γ = 90°
Volume	24413(4) Å^3	
Z	4	
Density (calculated)	1.107 Mg/m^3	
Absorption coefficient	0.532 mm^{-1}	
F(000)	8265	
Crystal size	0.17 x 0.13 x 0.07 mm^3	
Theta range for data collection	1.197 to 25.443°	
Index ranges	$-39 \leqq h \leqq 39$, $-48 \leqq k \leqq 48$, $-22 \leqq l \leqq 22$	
Reflections collected	123443	
Independent reflections	22972 [R(int) = 0.0868]	
Completeness to theta = 25.242°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	22972 / 470 / 1244	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2sigma(I)]	R_1 = 0.0822, wR_2 = 0.2189	
R indices (all data)	R_1 = 0.1313, wR_2 = 0.2606	
Absolute structure parameter	0.25(6)	
Largest diff. peak and hole	0.864 and –0.627 e·Å^{-3}	

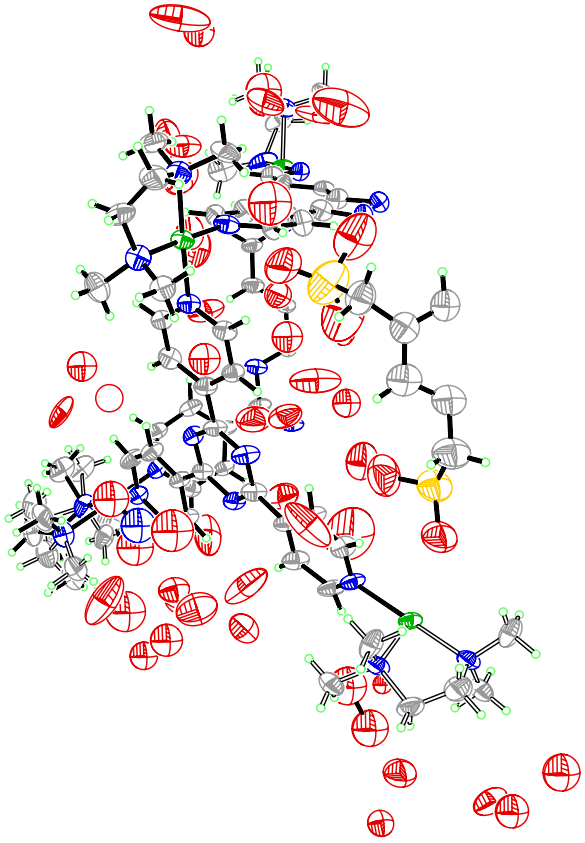


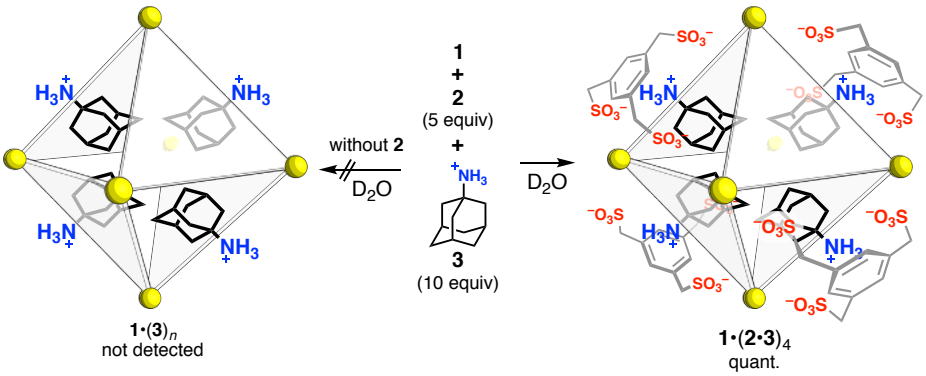
Figure S4. An ORTEP drawing (refinement structure, 30% probability ellipsoids) of **1·2**.

4. Inclusion of cationic guest 3 in cage 1 with the help of anion 2

Preparation of 1-adamantylammonium nitrate (3)

1-Adamantylamine (0.102 g, 0.672 mmol) was suspended in H_2O and neutralized by 1 M HNO_3. After filtration, the filtrate was concentrated under reduced pressure and dried *in vacuo*. 1-Adamantylammonium nitrate (**3**) was obtained as a white powder (0.128 g, 0.599 mmol, 89%).

Inclusion experiments in the presence and absence of anion 2



<u>In the absence of anion **2**</u>

To a D_2O solution of cage **1** (0.50 mM, 2.0 mL, 1 equiv) was added cationic guest **3** (2.15 mg, 10.0 μmol, 10 equiv). After stirred at room temperature for 1 h, the ^{1}H NMR spectrum of the reaction mixture was measured.

<u>In the presence of anion **2**</u>

To a D_2O solution of cage **1** (0.50 mM, 2.0 mL, 1 equiv) were added tripodal anion **2** (2.19 mg, 5.14 μmol, 5.1 equiv) and cationic guest **3** (2.13 mg, 9.94 μmol, 9.9 equiv). After stirred at room temperature for 1 h, the ^{1}H NMR spectrum of the reaction mixture was measured.

Chemical shift changes of 3 after inclusion

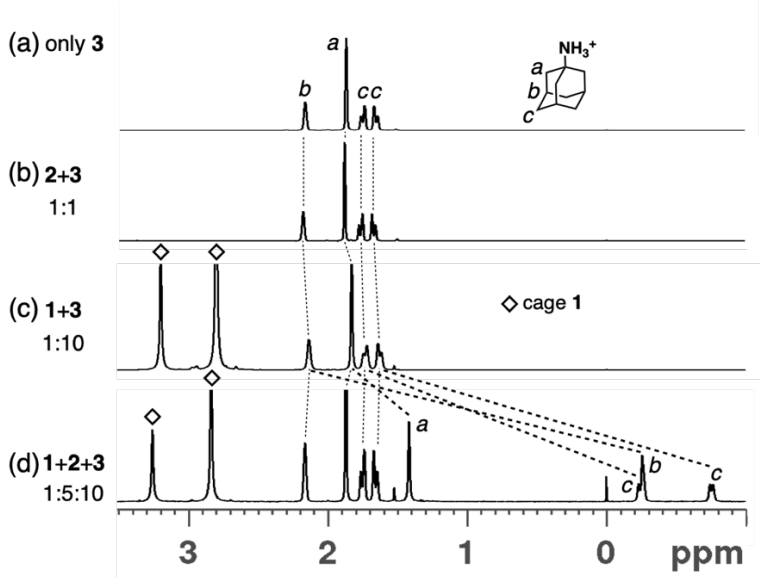
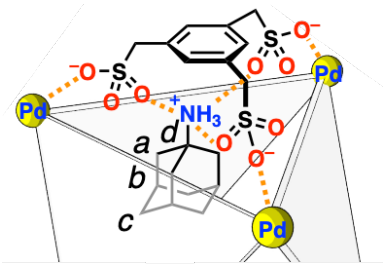


Figure S5. ^{1}H NMR spectra (500 MHz, D_2O, 300 K) of (a) guest **3**, (b) 1:1 mixture of **2** and **3**, (c) 1:10 mixture of **1** and **3**, and (d) 1:5:10 mixture of **1**, **2**, and **3**.



Physical data of 1:5:10 mixture of 1, 2, and 3: ^{1}H NMR (500 MHz, D_2O, 300K): δ = 9.70 (d, J = 6.0 Hz, 24H, **1**, PyH_{α}), 8.85 (d, J = 6.0 Hz, 24H, **1**, Py$H_{ß}$), 7.79 (s, 3H, **2**, ArH), 4.59 (s, 6H, **2**, CH_2), 3.27 (s, 24H, **1**, CH_2), 2.85 (s, 72H, **1**, CH_3), 2.17 (br, 3H, $\mathbf{3}_{free}$, H_b), 1.88 (br, 6H, $\mathbf{3}_{free}$, H_a), 1.77–1.65 (d, J = 12 Hz, 6H, $\mathbf{3}_{free}$, H_c), 1.42 (s, 6H, $\mathbf{3}_{included}$, H_a), –0.23 (overlapped, 3H, $\mathbf{3}_{included}$, H_c), –0.26 (s, 3H, $\mathbf{3}_{included}$, H_b), –0.75 (d, J = 10 Hz, 3H, $\mathbf{3}_{included}$, H_c); ^{13}C NMR (125MHz, D_2O, 300K): δ = 169.33 (**1**, ArC), 153.10 (**1**, ArC), 144.76 (**1**, ArC), 133.17(**2**, ArC), 133.13(**2**, ArC), 125.80(**1**, ArC), 63.20 (**1**, CH_2), 57.40 (**2**, CH_2), 52.44 ($\mathbf{3}_{free}$, C_d), 50.85 ($\mathbf{3}_{included}$, C_d), 50.72 (**1**, CH_3), 40.14 ($\mathbf{3}_{free}$, C_a), 38.78 ($\mathbf{3}_{included}$, C_a), 34.98 ($\mathbf{3}_{free}$, C_c), 34.08 ($\mathbf{3}_{included}$, C_c), 28.91 ($\mathbf{3}_{free}$, C_b), 27.70 ($\mathbf{3}_{included}$, C_b).

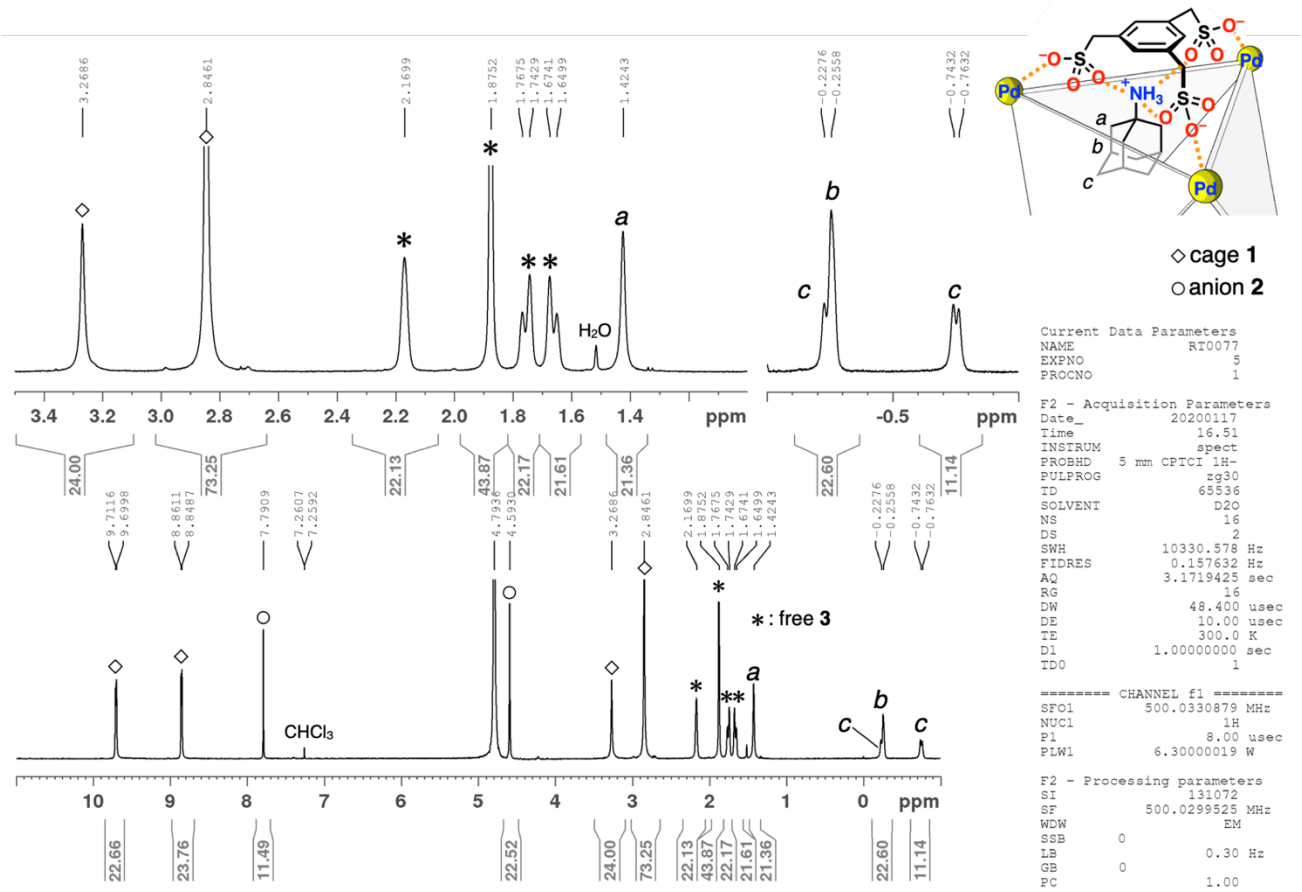


Figure S6. ^{1}H NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:10 mixture of **1**, **2**, and **3**.

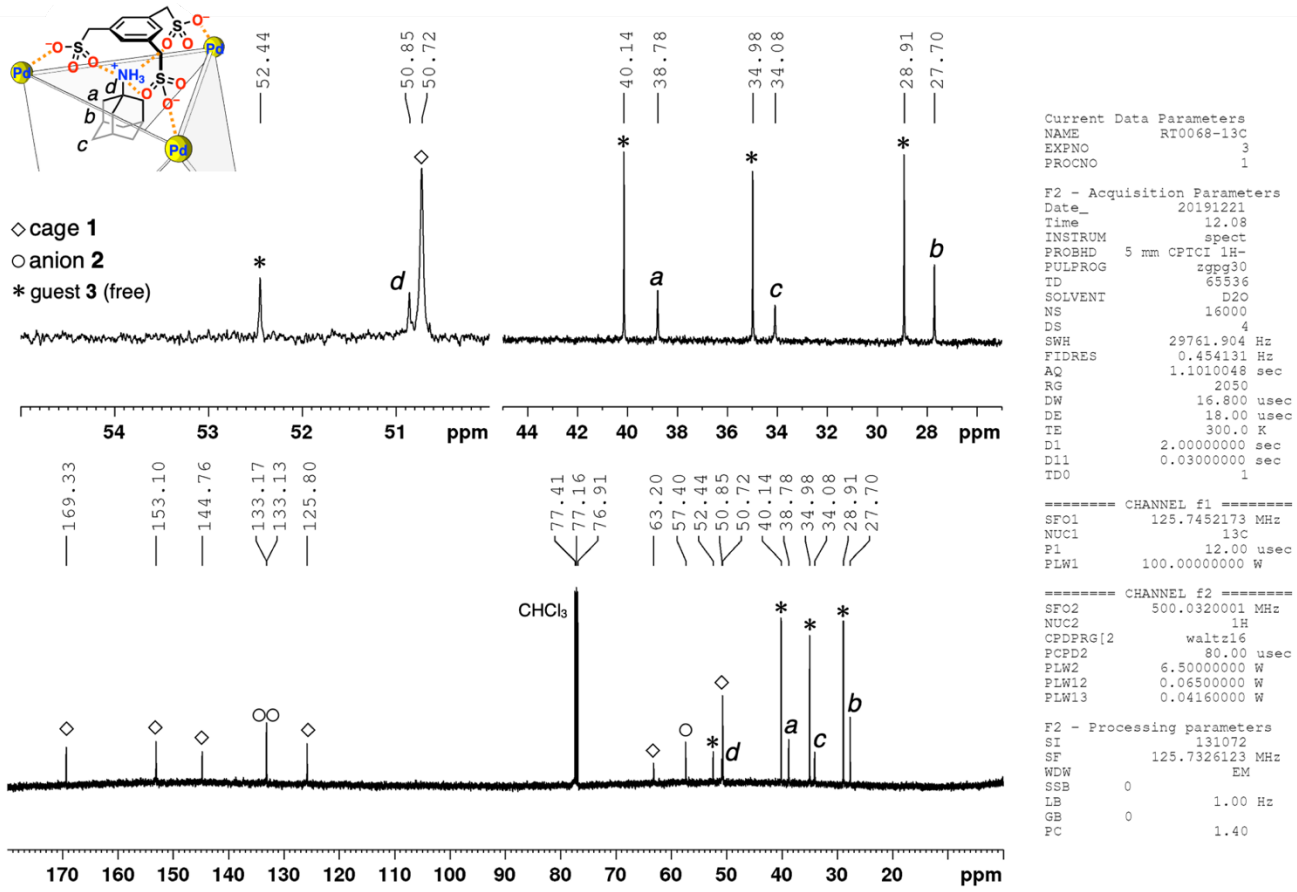


Figure S7. ^{13}C NMR spectrum (125 MHz, D_2O, 300 K) of 1:5:10 mixture of **1**, **2**, and **3**.

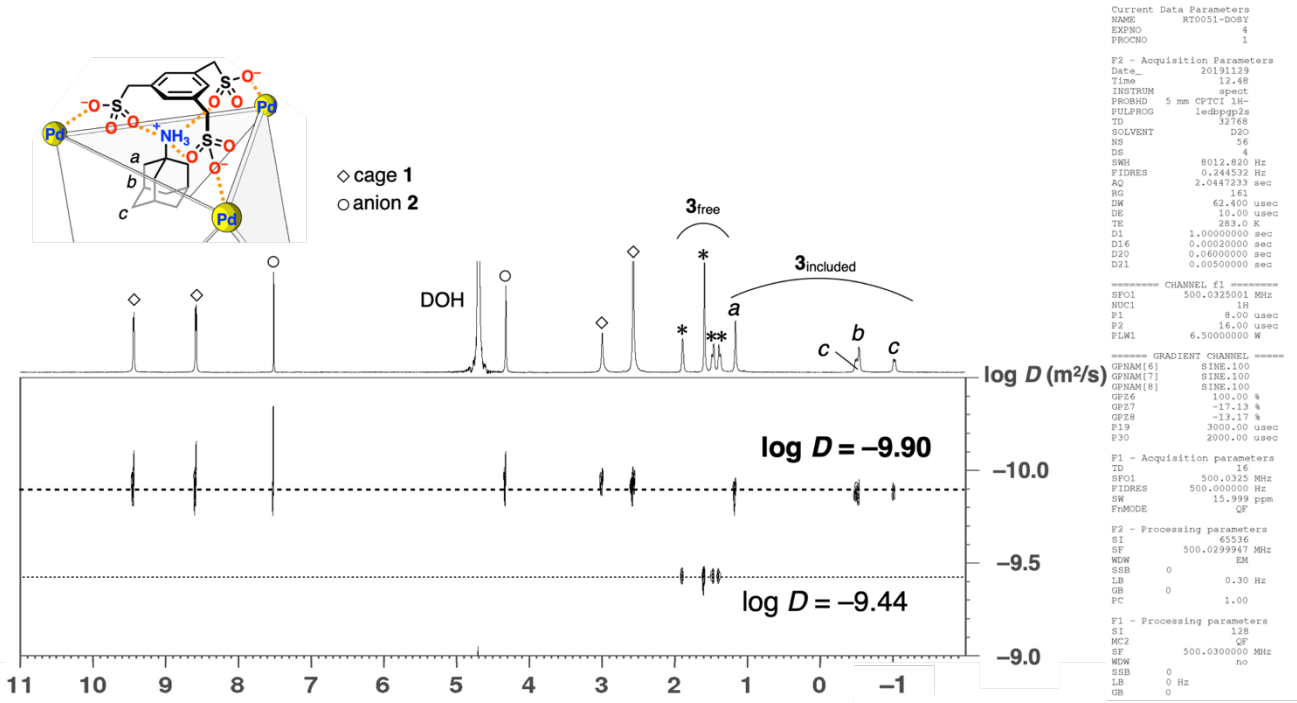


Figure S8. ^{1}H DOSY NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:10 mixture of **1**, **2**, and **3** (diffusion time: 60 ms, length of diffusion gradient: 2 ms, number of increments: 16, number of scans: 56, processing method: exponential).

Comparison with different amounts of trianion 2

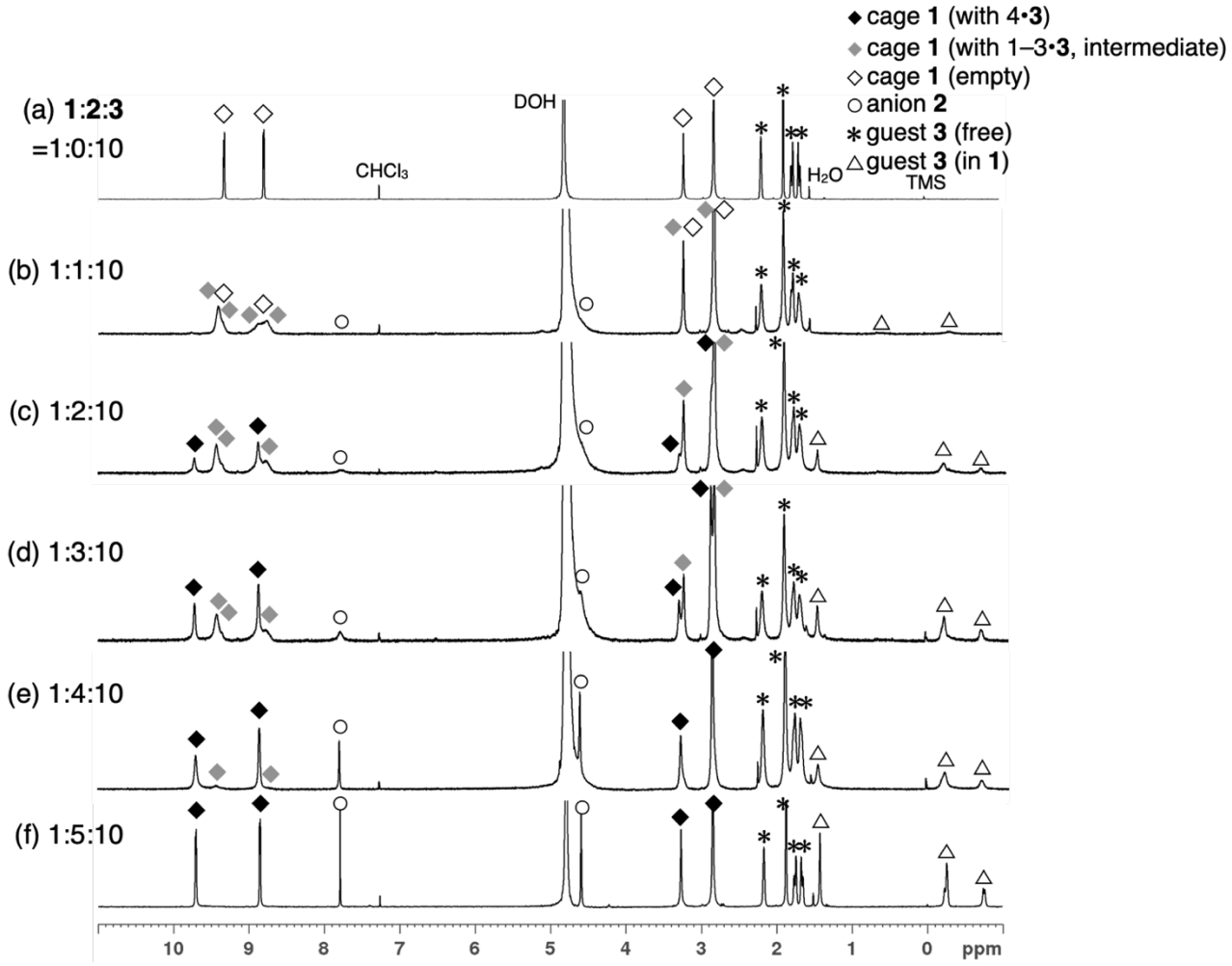


Figure S9. ^{1}H NMR spectra (500 MHz, D_2O, 300 K) of mixture of **1**, **2**, and **3**.

5. X-ray crystallographic analyses of 1·(2·3)$_4$

1:5:10 mixture of **1**, **2**, and **3** (chloride salt) was stood at 50 ºC and the water solvent was allowed to evaporate. After two weeks, a single crystal suitable for X-ray diffraction analysis was obtained.

Crystal data for 1·(2·3)$_4$

Table S2. Crystal data and structure refinement for 1·(2·3)$_4$

Identification conde	p-1	
CCDC number	2022051	
Empirical formula	$C_{193}H_{260}N_{40}O_{72.89}Pd_6S_{15}$	
Formula weight	5425.97	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 18.67(3) Å	α = 87.008(14)°
	b = 21.20(3) Å	β = 89.552(15)°
	c = 33.52(5) Å	γ = 71.508(15)°
Volume	12563(31)Å^3	
Z	2	
Density (calculated)	1.434 Mg/m^3	
Absorption coefficient	0.632 mm^{-1}	
F(000)	5594	
Crystal size	0.17 x 0.05x 0.04 mm^3	
Theta range for data collection	1.150 to 21.396°.	
Index ranges	$-18 \leqq h \leqq 18$, $-21 \leqq k \leqq 21$, $-33 \leqq l \leqq 33$	
Reflections collected	78181	
Independent reflections	27180 [R(int) = 0.2360]	
Completeness to theta = 21.396°	95.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	27180 / 1160 / 3117	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R_1 = 0.1129, wR_2 = 0.2997	
R indices (all data)	R_1 = 0.2731, wR_2 = 0.3928	
Largest diff. peak and hole	1.097 and –0.913 e·Å^{-3}	

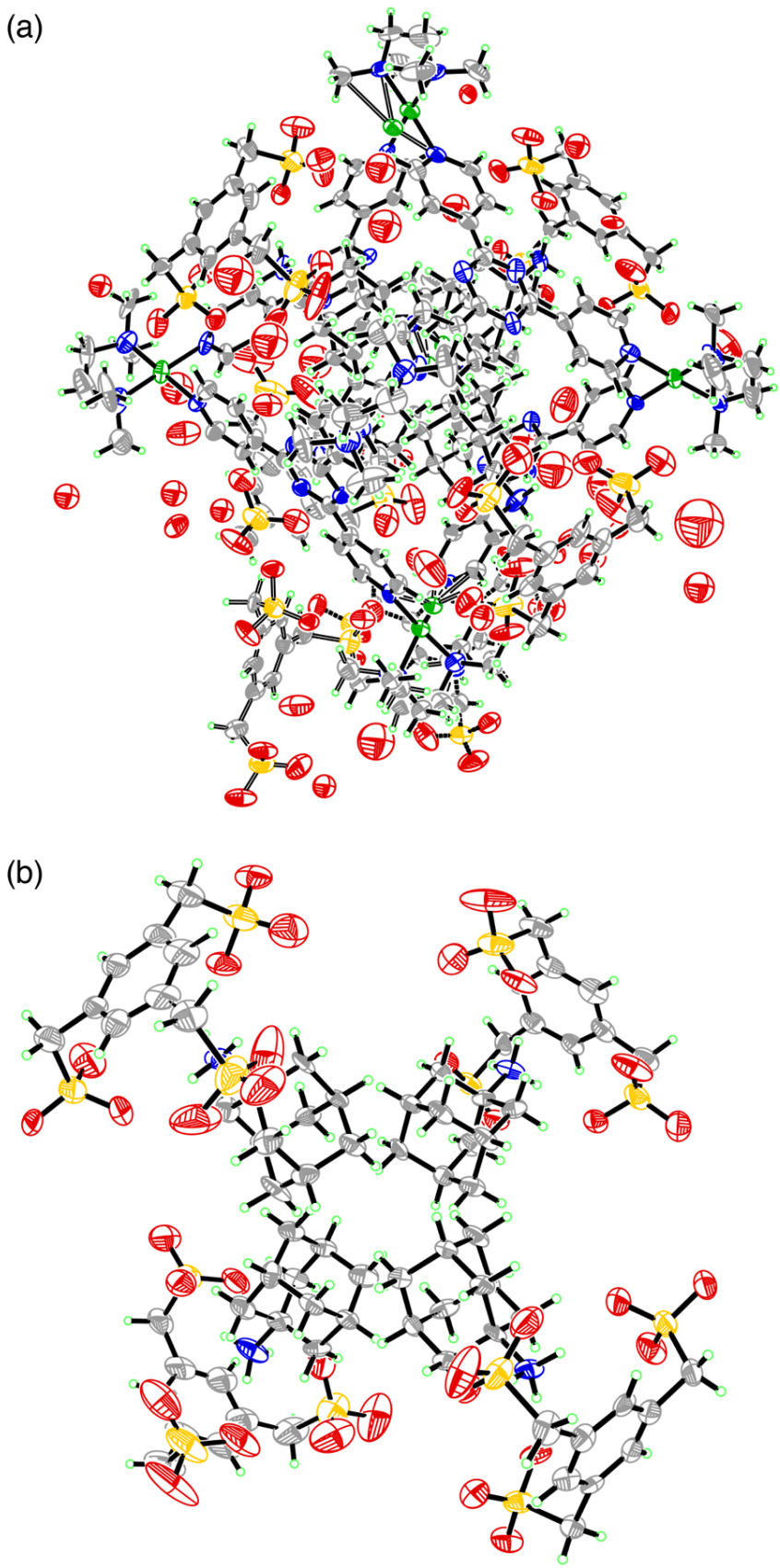


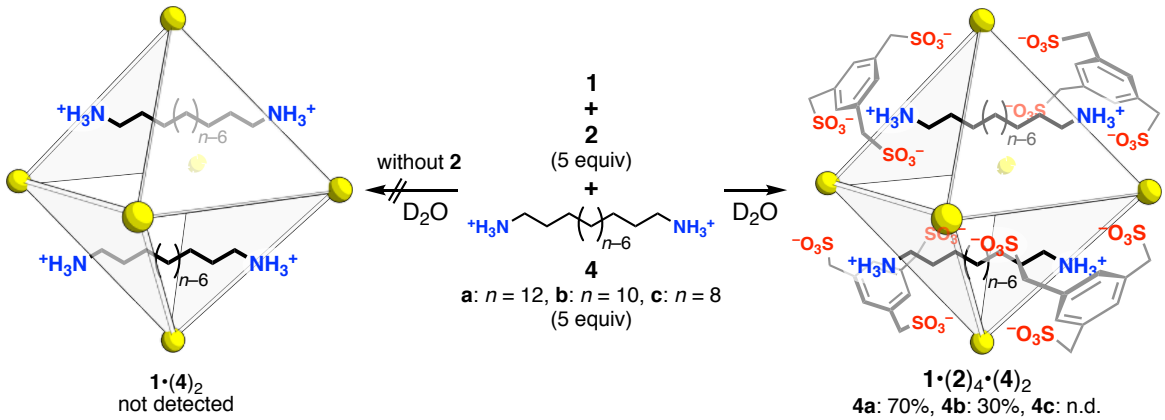
Figure S10. ORTEP drawings (30% probability ellipsoids) of (a) the refinement structure and (b) the guests (**2** and **3**) in **1**·(**2**·**3**)$_4$.

6. Inclusion of cationic substrates 4a–c in cage 1 with the help of anion 2

General procedure for preparation of cationic substrates

1,ω-Alkanediamine (0.196–0.285 mmol) was suspended in H_2O and neutralized by 1 M HNO_3. After filtration, the solvent water was removed *in vacuo* to give 1,ω-alkanediammonium dinitrate as a white powder in quantitative yield.

General procedure of inclusion experiments in the presence and absence of anion 2



<u>In the absence of anion **2**</u>

To a D_2O solution of cage **1** (1.0 mM, 1.0 mL, 1 equiv) was added cationic guest **4** (1.51–1.58 mg, 4.84–5.59 μmol, 4.8–5.6 equiv). After stirred at room temperature for 1 h, the ^{1}H NMR spectrum of the reaction mixture was measured.

<u>In the presence of anion **2**</u>

To a D_2O solution of cage **1** (1.0 mM, 1.0 mL, 1 equiv) were added tripodal anion **2** (2.14–2.16 mg, 5.02–5.07 μmol, 5.0–5.1 equiv) and cationic guest **4** (1.46–1.66 mg, 5.09–5.40 μmol, 4.7–5.5 equiv). After stirred at room temperature for 1 h, the ^{1}H NMR spectra of the reaction mixtures were measured.

Chemical shift changes of 4 after inclusion

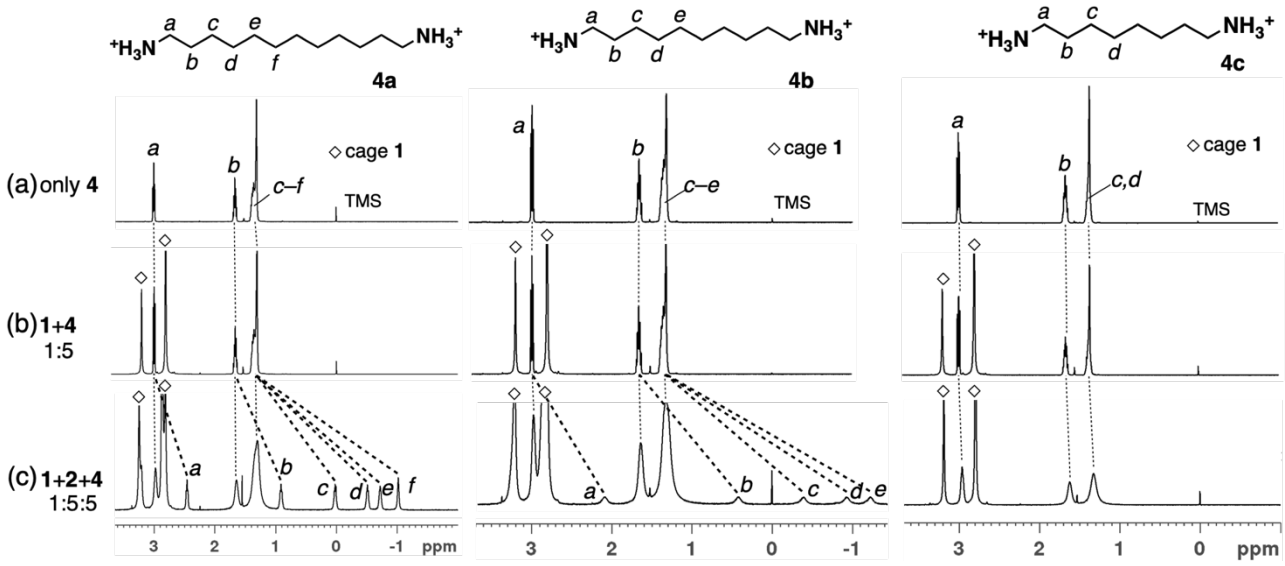
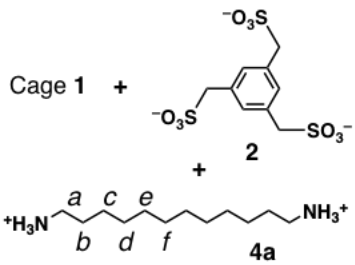


Figure S11. ^{1}H NMR spectra (500 MHz, D_2O, 300 K) of (a) guest **4**, (b) 1:5 mixture of **1** and **4**, and (c) 1:5:5 mixture of **1**, **2**, and **4**.



Physical data of 1:5:5 mixture of 1, 2, and 4a: ^{1}H NMR (500 MHz, D_2O, 300K): δ = 9.68 (br, 8H, **1**, PyH_α), 9.61 (br, 8H, **1**, PyH_α), 9.57 (br, 8H, **1**, PyH_α), 9.41 (br, 24H, **1** (empty), PyH_α) 8.81 (br, 24H, **1**, PyH_β), 7.67 (s, 3H, **2**, ArH), 4.45 (s, 6H, **2**, CH_2), 3.24 (s, 24H, **1**, CH_2), 3.23 (s, 24H, **1** (empty), CH_2), 2.97 (br, 4H, **4a**$_{free}$, H_a), 2.86 (s, 72H, **1**, CH_3), 2.81 (s, 72H, **1** (empty), CH_3), 2.45 (m, 4H, **4a**$_{included}$, H_a), 1.63 (br, 4H, **4a**$_{free}$, H_b), 1.29 (br, 16H, **4a**$_{free}$, $H_{c–f}$), 0.90 (br, 4H, **4a**$_{included}$, H_b), 0.01 (br, 4H, **4a**$_{included}$, H_c), –0.52 (br, 4H, **4a**$_{included}$, H_d), –0.73 (br, 4H, **4a**$_{included}$, H_e), –1.03 (br, 4H, **4a**$_{included}$, H_f).

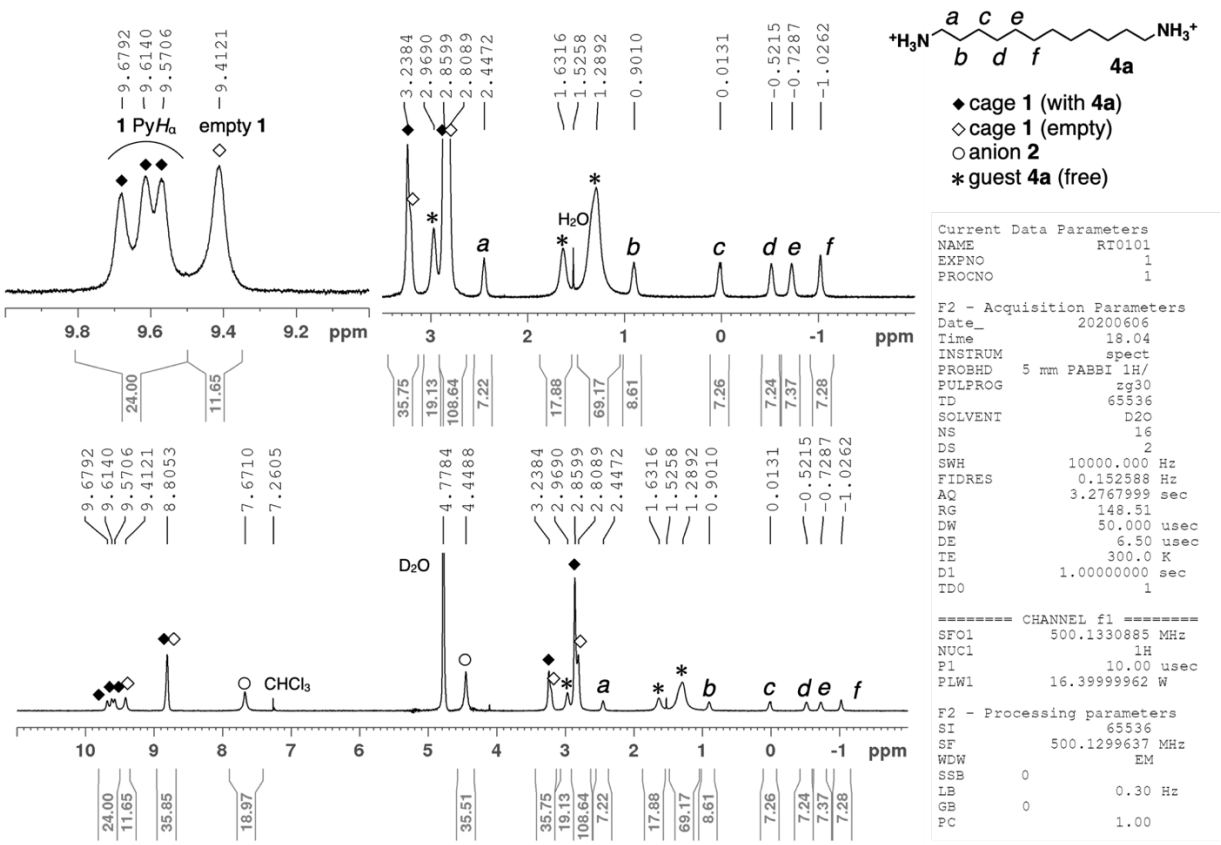


Figure S12. ^{1}H NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:5 mixture of **1**, **2**, and **4a**.

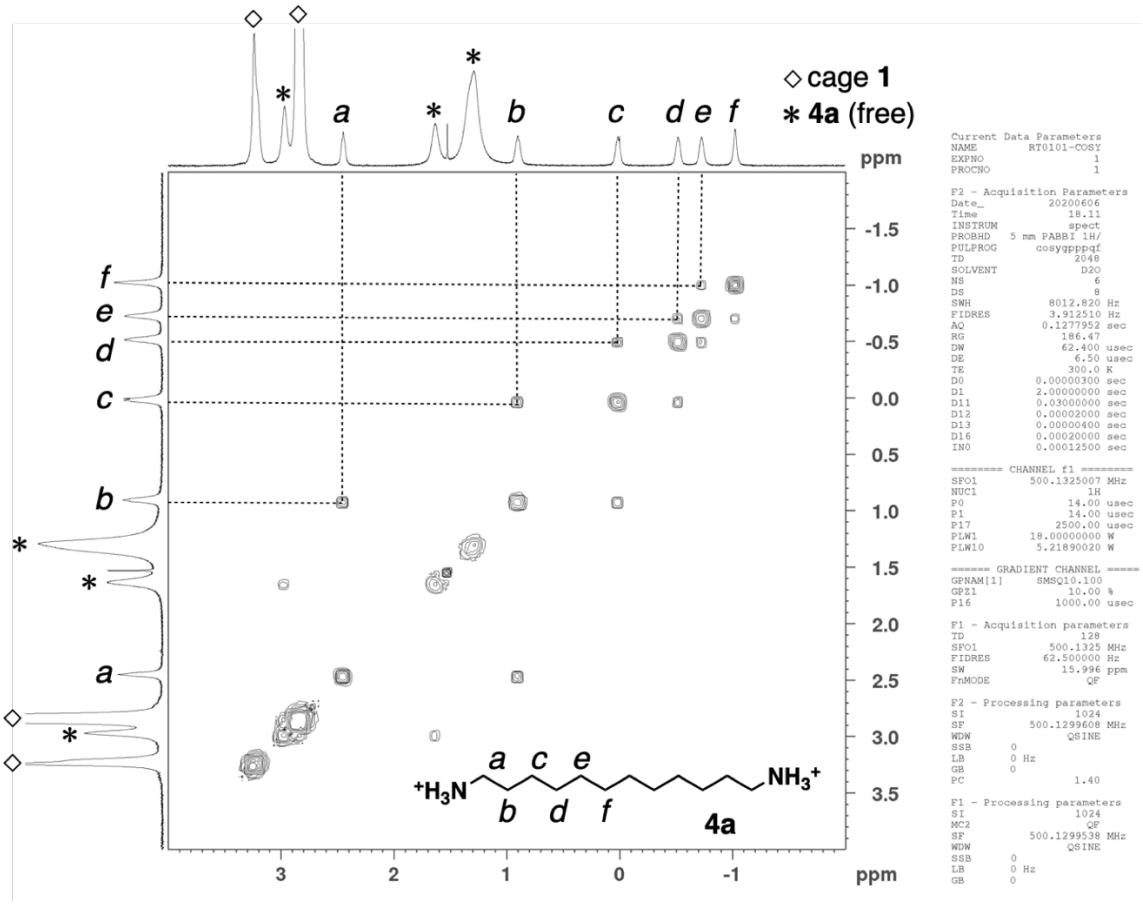
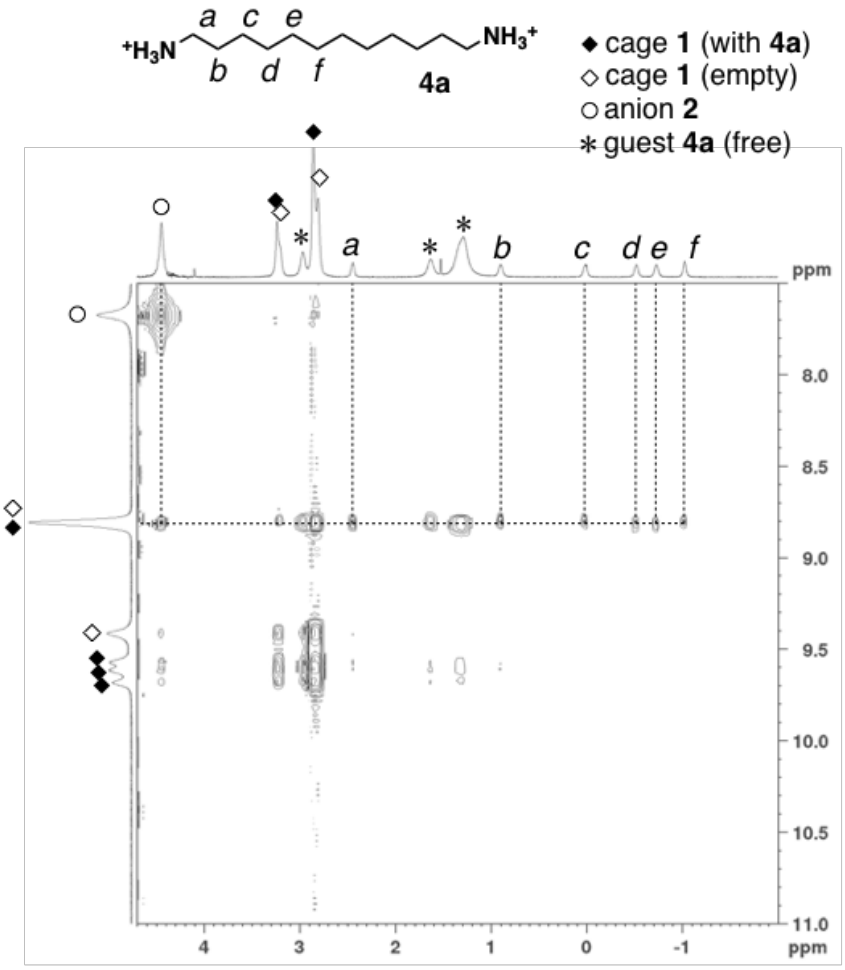


Figure S13. ^{1}H–^{1}H COSY NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:5 mixture of **1**, **2**, and **4a**.

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DW                62.400 usec
DE                 10.00 usec
TE                 300.0 K
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D8            0.30000001 sec
D16           0.00020000 sec
IN0           0.00012500 sec

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NUC1                  1H
P1                  8.00 usec
P2                 16.00 usec
PLW1          6.50000000 W

====== GRADIENT CHANNEL =====
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GPZ1               40.00 %
P16              1000.00 usec

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FIDRES         31.250000 Hz
SW                15.999 ppm
FnMODE       States-TPPI

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SSB                     2
LB        0 Hz
GB        0
PC                  1.00

F1 - Processing parameters
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WDW                 QSINE
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GB        0
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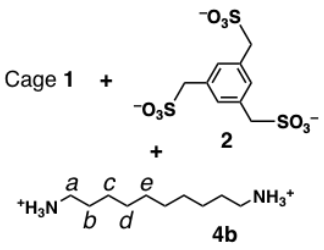
Figure S14. ^{1}H-^{1}H NOESY NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:5 mixture of **1**, **2**, and **4a**.



Physical data of 1:5:5 mixture of 1, 2, and 4b: ^{1}H NMR (500 MHz, D_2O, 300K): δ = 9.64 (br, 24H, **1**, PyH_α), 9.40 (br, 24H, **1** (empty), PyH_α) 8.79 (br, 24H, **1**, Py$H_ß$), 7.64 (s, 3H, **2**, ArH), 4.42 (s, 6H, **2**, CH_2), 3.21 (s, 24H, **1**, CH_2), 2.98 (br, 4H, **4b**$_{free}$, H_a), 2.82 (s, 72H, **1**, CH_3), 2.08 (br, 4H, **4b**$_{included}$, H_a), 1.64 (br, 4H, **4b**$_{free}$, H_b), 1.31 (br, 12H, **4b**$_{free}$, $H_{c–e}$), 0.42 (br, 4H, **4b**$_{included}$, H_b), –0.40 (br, 4H, **4b**$_{included}$, H_c), –0.94 (br, 4H, **4b**$_{included}$, H_d), –1.23 (br, 4H, **4b**$_{included}$, H_e).

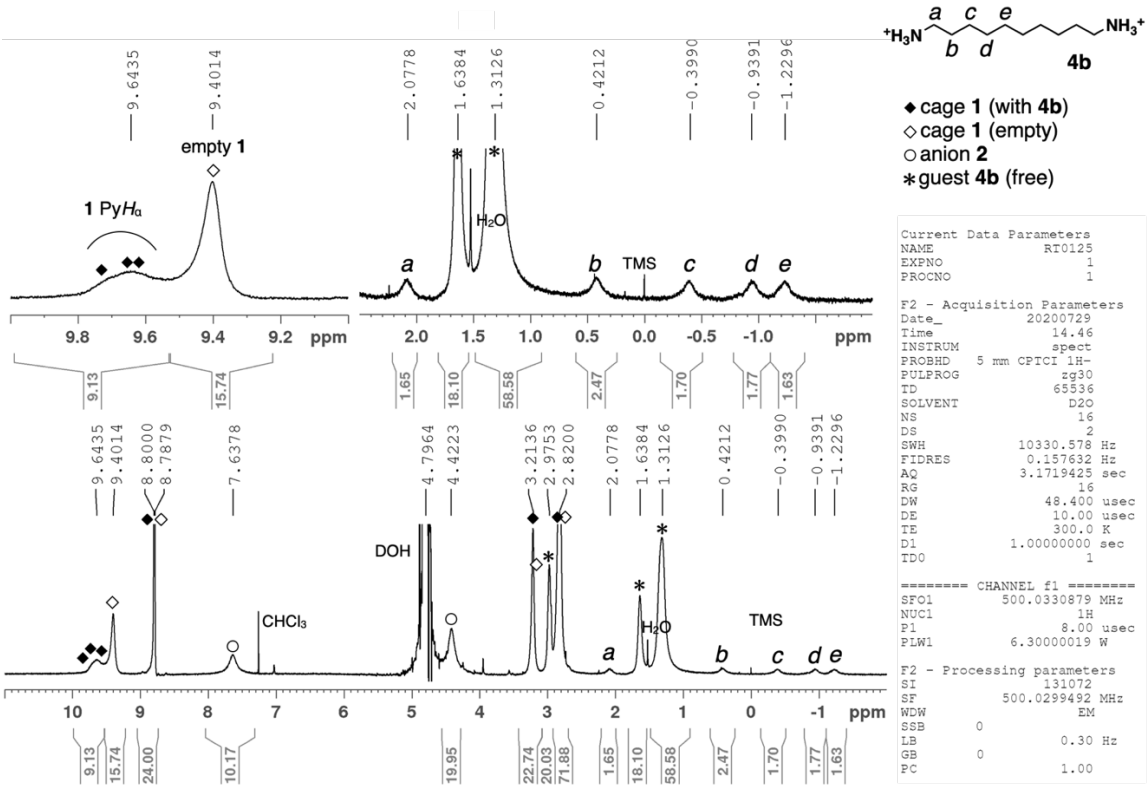


Figure S15. ^{1}H NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:5 mixture of **1**, **2**, and **4b**.

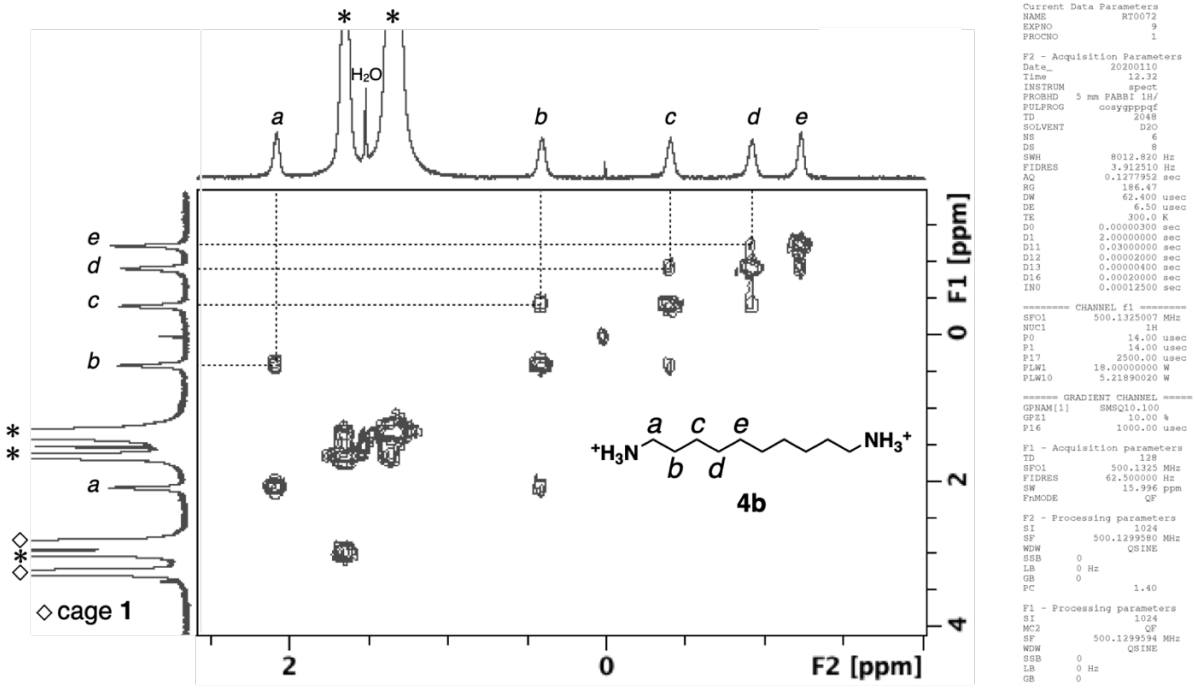
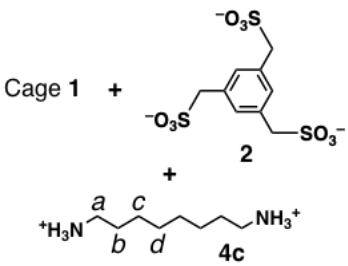


Figure S16. ^{1}H–^{1}H COSY NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:5 mixture of **1**, **2**, and **4b**.



Physical data of 1:5:5 mixture of 1, 2, and 4c: ^{1}H NMR (500 MHz, D_2O, 300K): δ = 9.39 (d, J = 6.2 Hz, 24H, **1**, PyH_α), 8.78 (d, J = 6.2 Hz, 24H, **1**, Py$H_ß$), 7.50 (br, 3H, **2**, ArH), 4.26 (br, 6H, **2**, CH_2), 3.19 (s, 24H, **1**, CH_2), 2.96 (br t, 4H, **4c**$_{free}$, H_a), 2.79 (s, 72H, **1**, CH_3), 1.62 (br, 4H, **4c**$_{free}$, H_b), 1.32 (br, 8H, **4c**$_{free}$, $H_{c\text{-}d}$).

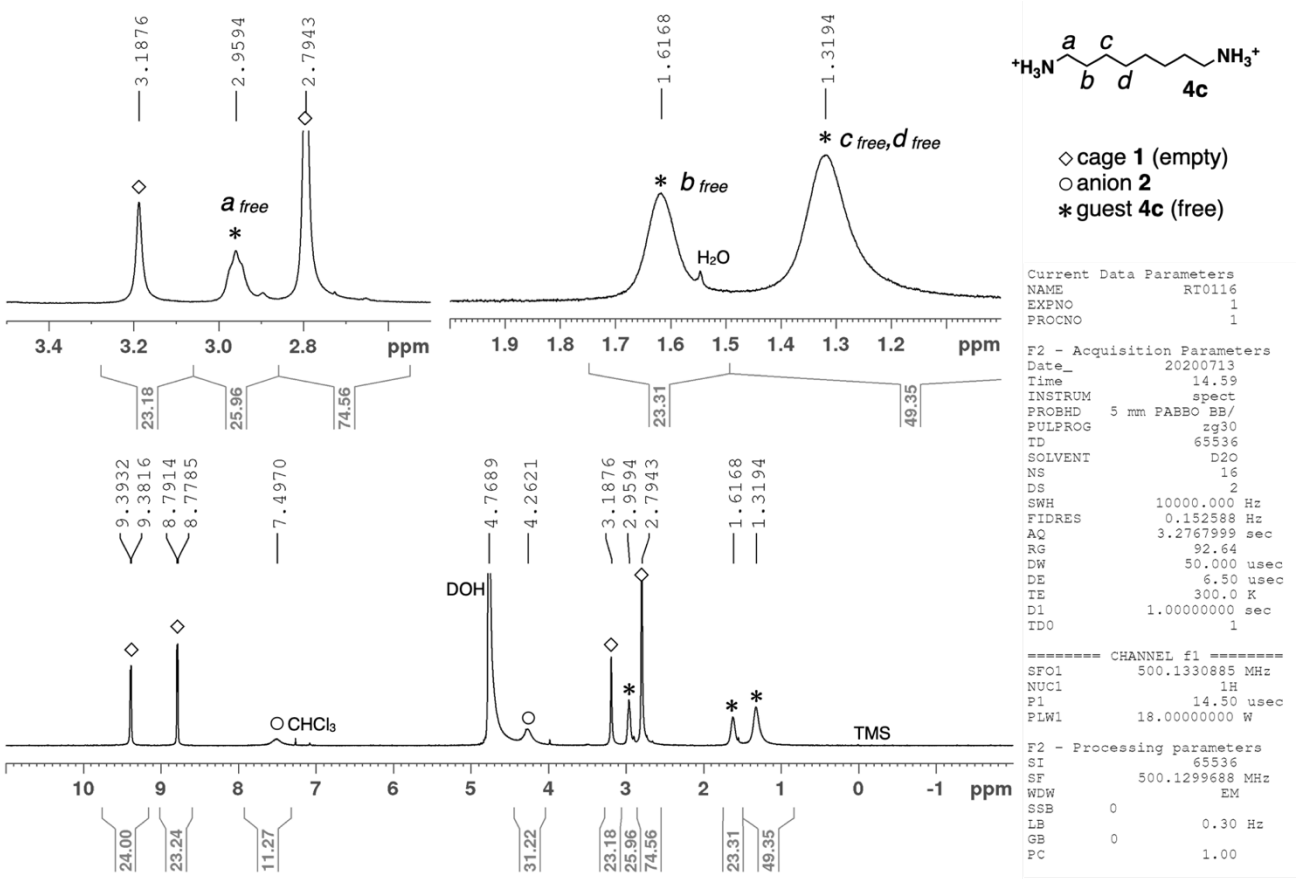
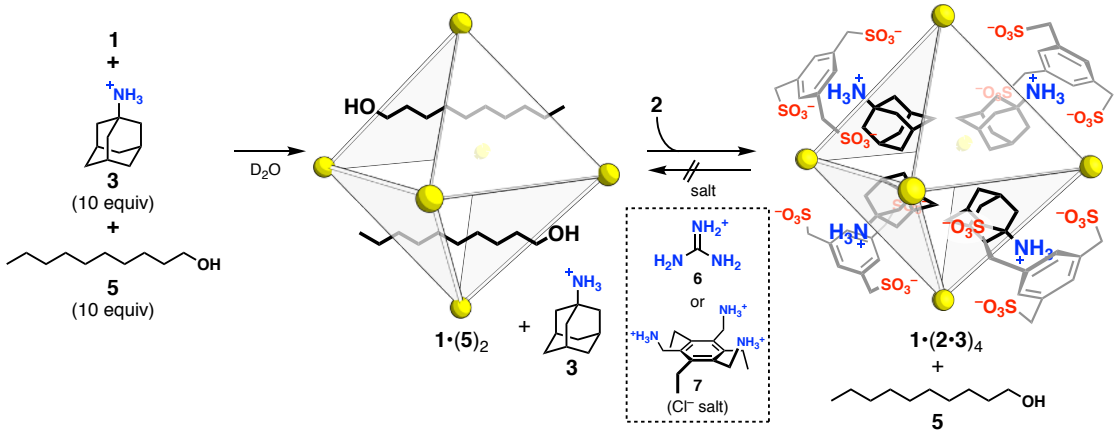


Figure S17. ^{1}H NMR spectrum (500 MHz, D_2O, 300 K) of 1:5:5 mixture of **1**, **2**, and **4c**.

7. Manipulative guest exchange by attaching of tripodal anion 2



Procedure of guest exchange

To a D_2O solution of cage **1** (0.50 mM, 2.0 mL, 1 equiv) was added cationic guest **3** (2.12 mg, 9.89 μmol, 9.9 equiv) and neutral alcohol **5** (1.9 μL, 9.96 μmol, 10 equiv). After stirred at room temperature for 1 h, tripodal anion **2** (2.09 mg, 4.90 μmol, 4.9 equiv) was added to reaction mixture. After stirred at room temperature for 1 h, ^{1}H NMR spectrum of the reaction mixture was measured.

Attempt to detach anion 2 from 1·(2·3)$_4$

After guest exchange, to reaction mixture of **1**, **2**, **3**, and **5** was added triangular cation **6** (6.18 mg, 64.7 μmol, 65 equiv). After stirred at room temperature for 1 h, ^{1}H NMR spectrum of the reaction mixture was measured. In other approach, equivalent of guest **5** was increased (10-times) and tripodal cation **7** (3.75 mg, 10.5 μmol, 10 equiv) was added.

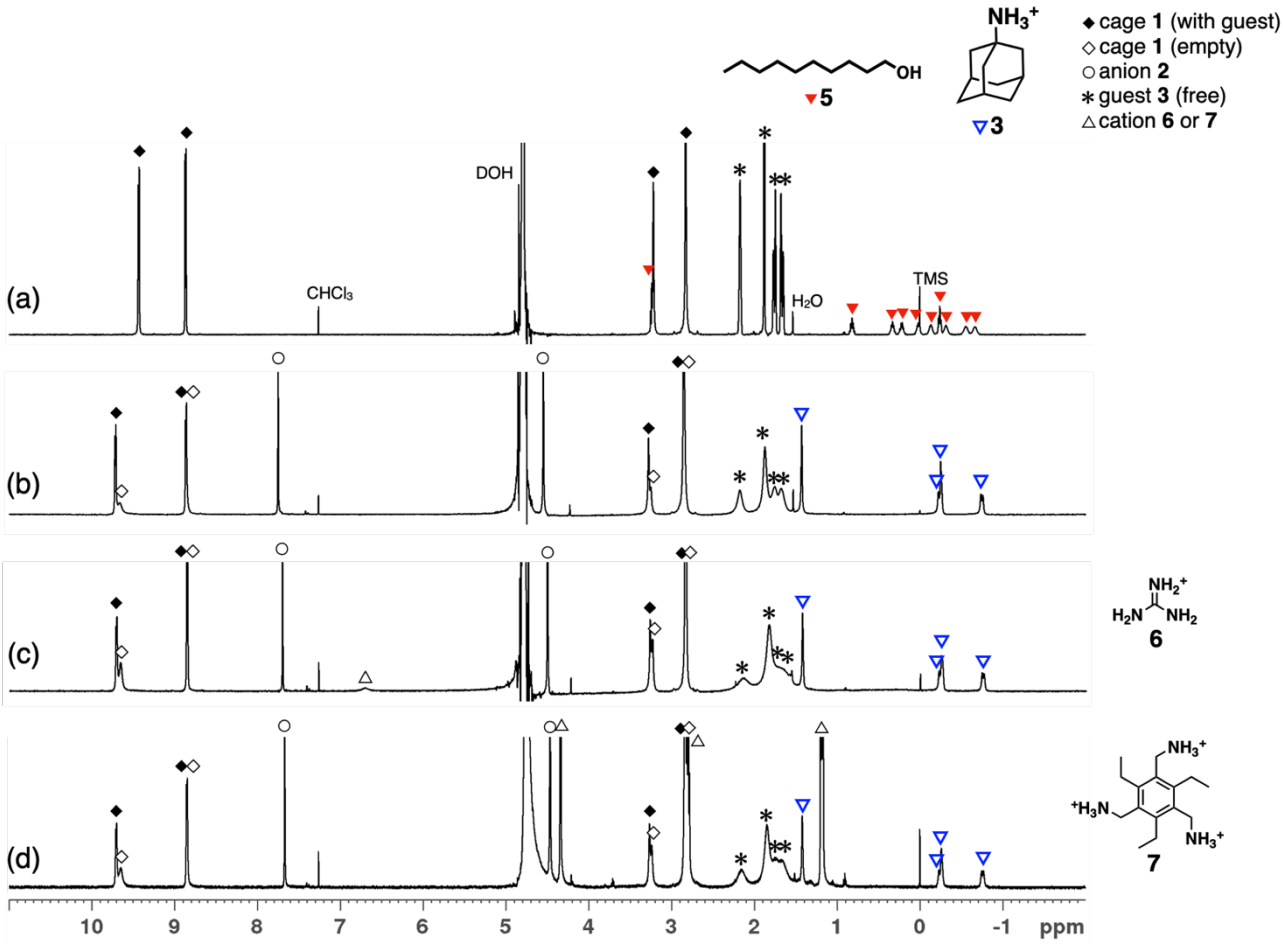


Figure S18. ^{1}H NMR spectra (500 MHz, D_2O, 300 K) of the mixtures of (a) **1** (1 equiv), **3** (10 equiv), and **5** (10 equiv), (b) **1**, **2** (5 equiv), **3** (10 equiv), and **5** (10 equiv), (c) **1**, **2** (5 equiv), **3** (10 equiv), **5** (10 equiv), and **6** (excess), and (d) **1**, **2** (5 equiv), **3** (10 equiv), **5** (100 equiv), and **7** (excess).

[References]

1. Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. Self-Assembly of Ten Molecules into Nanometre-Sized Organic Host Frameworks. *Nature* **1995**, *378*, 496–471.
2. Dalrymple, S. A.; Parvez, M.; Shimizu, G. K. H. Intra- and Intermolecular Second-Sphere Coordination Chemistry: Formation of Capsules, Half-Capsules, and Extended Structures with Hexaaquo- and Hexaamminemetal Ions. *Inorg. Chem.* **2002**, *41*, 6986–6996.
3. Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 3–8.
4. Hübschle, C. B.; Sheldrick, G. M.; Dittrich, B. ShelXle : A Qt Graphical User Interface for SHELXL. *J. Appl. Crystallogr.* **2011**, *44*, 1281–1284.
5. Spek, A. L. PLATON SQUEEZE: A Tool for the Calculation of the Disordered Solvent Contribution to the Calculated Structure Factors. *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 9–18.