Controlled Release of the Guest Molecule via Borate Formation of Fluorinated Boronic Ester Cage

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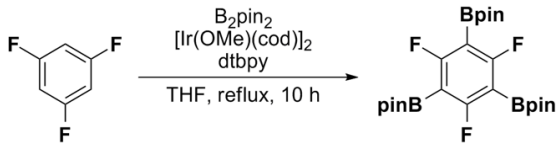
1. General methods

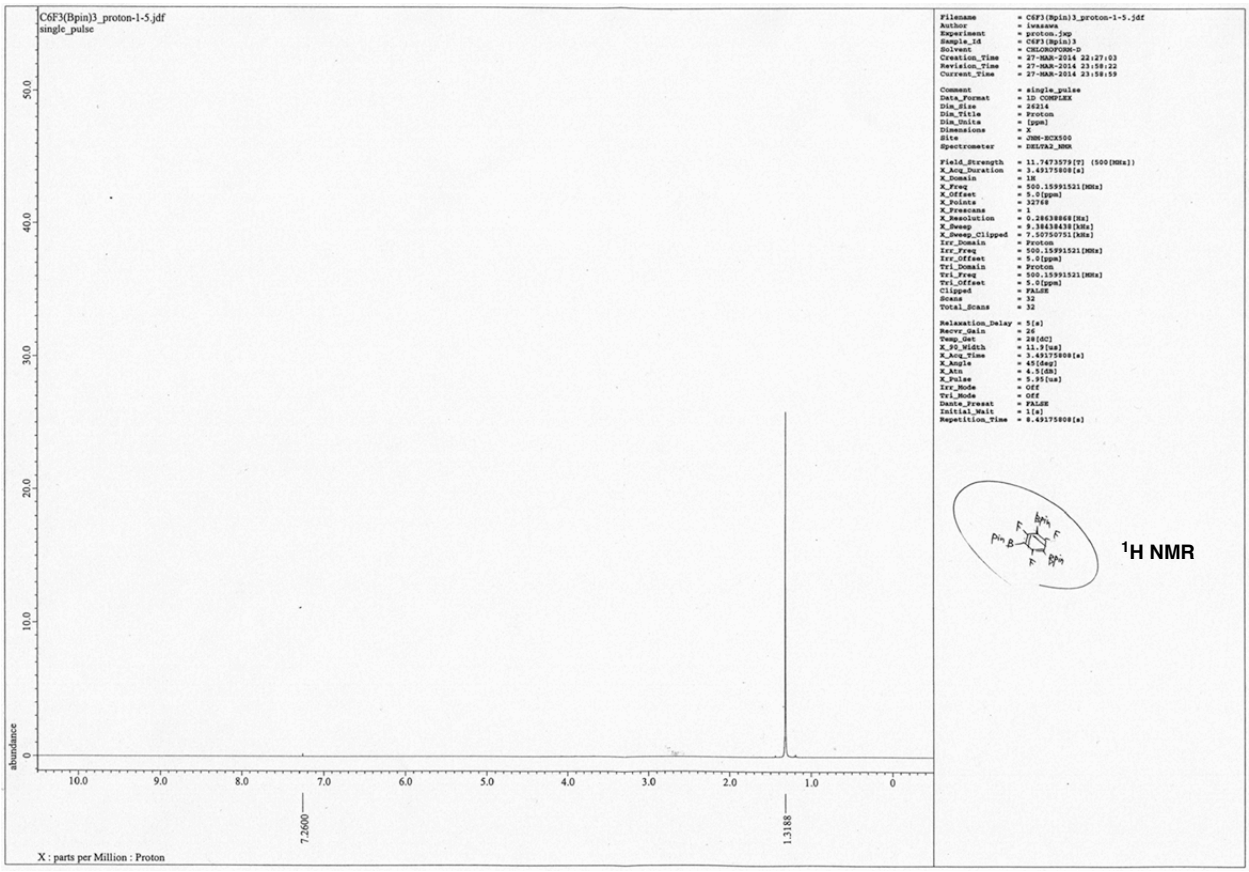
All operations were performed under air unless otherwise noted. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL AL-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C), a JEOL AL-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) or a JEOL Lamda-300 (75 MHz for ^{13}C) spectrometer using $CHCl_3$ (^{1}H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.0) as an internal standard. ^{11}B NMR spectra were recorded on a JEOL ECX-400 (127 MHz) spectrometer using $BF_3 \cdot OEt_2$ (^{11}B, δ = 0.00) as an external standard. IR spectra were recorded on an IR-810 or an FT/IR-460 plus (JASCO Co., Ltd). Tetrahydrofuran (THF) was purified by solvent system of Glass-Contour. Other solvents were distilled according to the usual procedures and stored over molecular sieves unless otherwise noted. High resolution mass analyses (FAB) were performed on a JEOL JMS-700 mass spectrometer using (2-nitrophenyl)octylether or NBA as a matrix. Elemental analyses were performed on a Perkin-Elmer 2400 instrument. Isothermal titration calorimetry (ITC) measurements were performed on a MicroCal system, iTC_{200} model (DKSH Japan Co., Ltd.). *o*-xylene@*homo*-**[3+2]-H_6** was prepared by recrystallization of *homo*-**[4+2]-H_6**[S1] from *o*-xylene. Racemic tetrol **1** was prepared according to the literature procedure.[S2]

2. Preparation of 2,4,6-trifluoro-1,3,5-benzenetriboronic tris(pinacol) ester 2

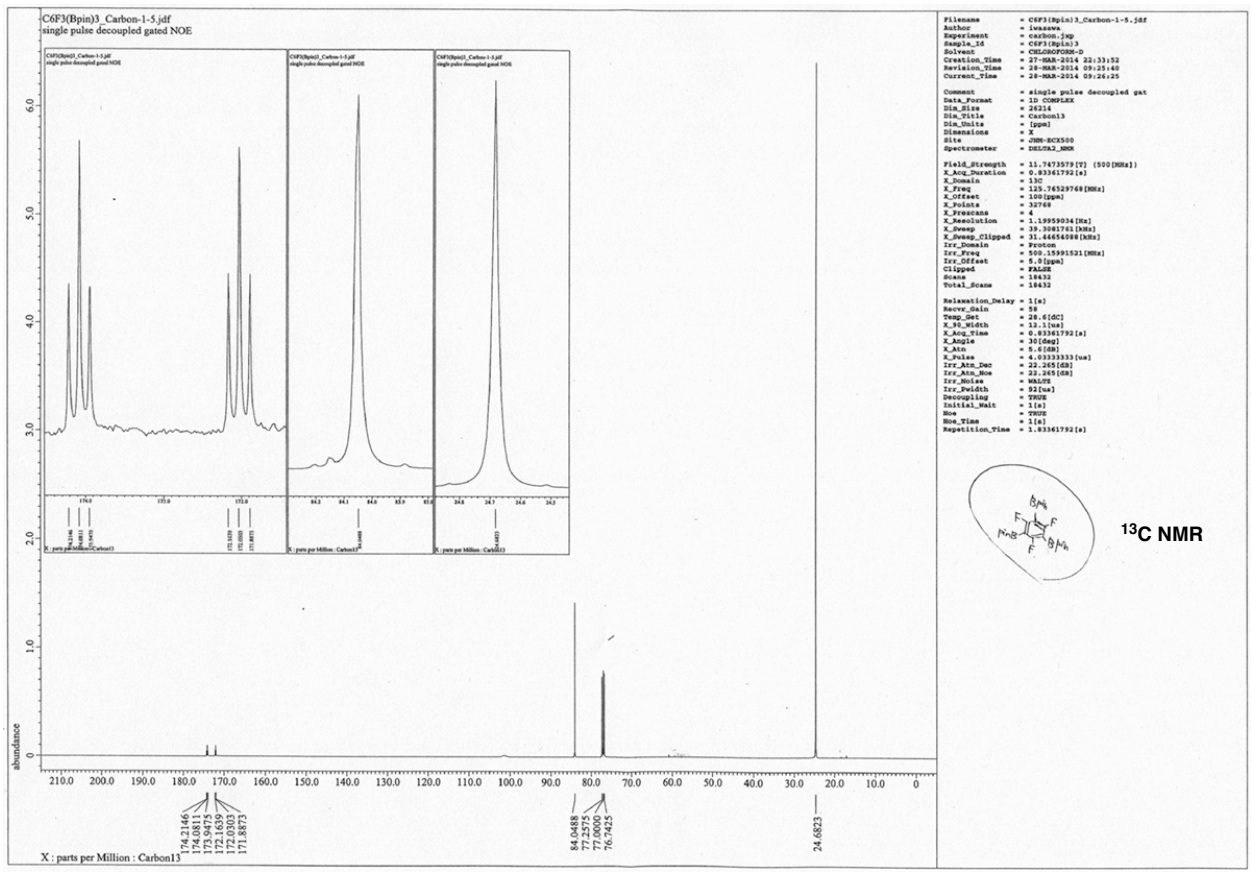


86 %

1,3,5-Trifluorobenzene (0.21 mL, 2.0 mmol), bis(pinacolato)diboron (2.44 g, 9.61 mmol), $[Ir(OMe)(cod)]_2$ (40.0 mg, 0.060 mmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (32.2 mg, 0.120 mmol) were mixed in THF (6.0 mL) under Ar. The mixture was refluxed for 10 h. The mixture was cooled and the solvent was removed under vacuum. The crude product was washed with *n*-hexane to remove unreacted B_2pin_2. Recrystallization from ethanol afforded the pure product (877 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1 (dt, J = 256, 16.7 Hz), 101.5, 84.0, 24.7; IR (ATR): 2978, 1590, 1384, 1373, 1325, 1273, 1140, 966, 873, 846, 786, 743, 681, 668, 655 cm^{-1}; HR-MS (FAB, *m/z*): $[M]^+$ calcd. for $C_{24}H_{36}B_3F_3O_6$, 510.2743; found, 510.2856.

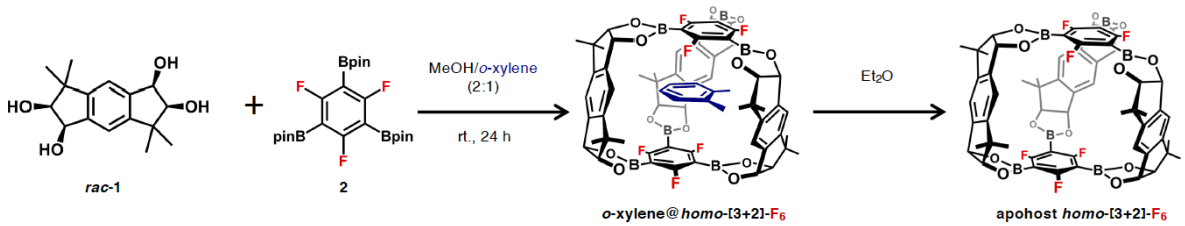


^{1}H NMR



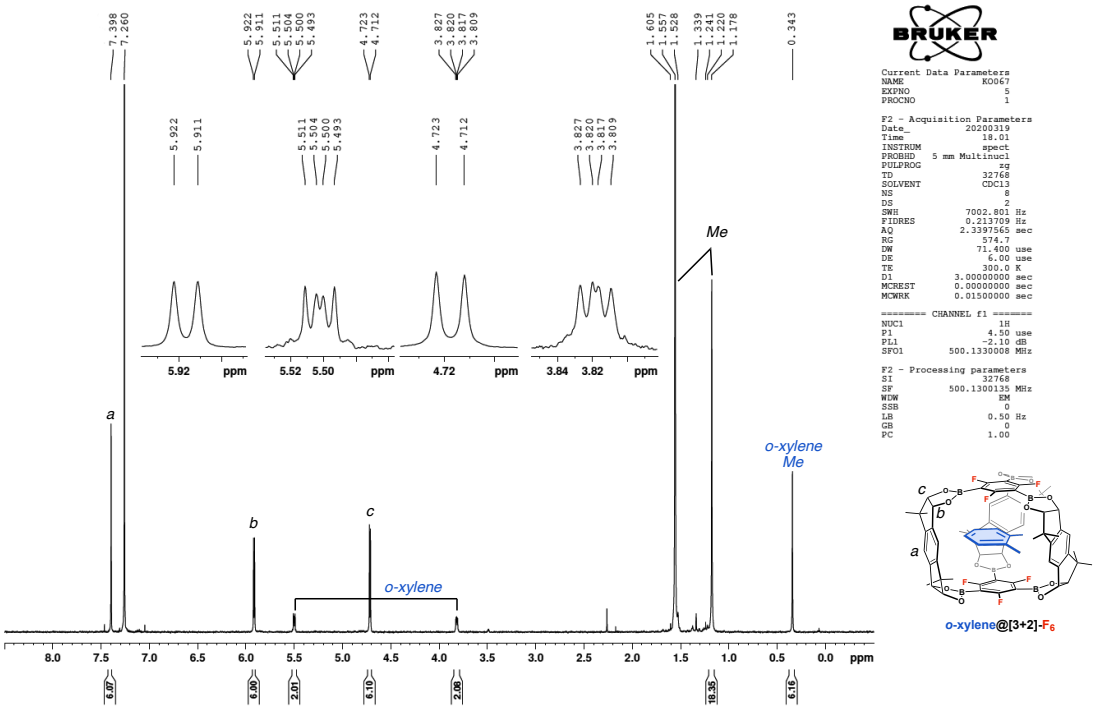
^{13}C NMR

3. Self-assembly of *o*-xylene@*homo*-[3+2]-F_6 and preparation of apohost *homo*-[3+2]-F_6



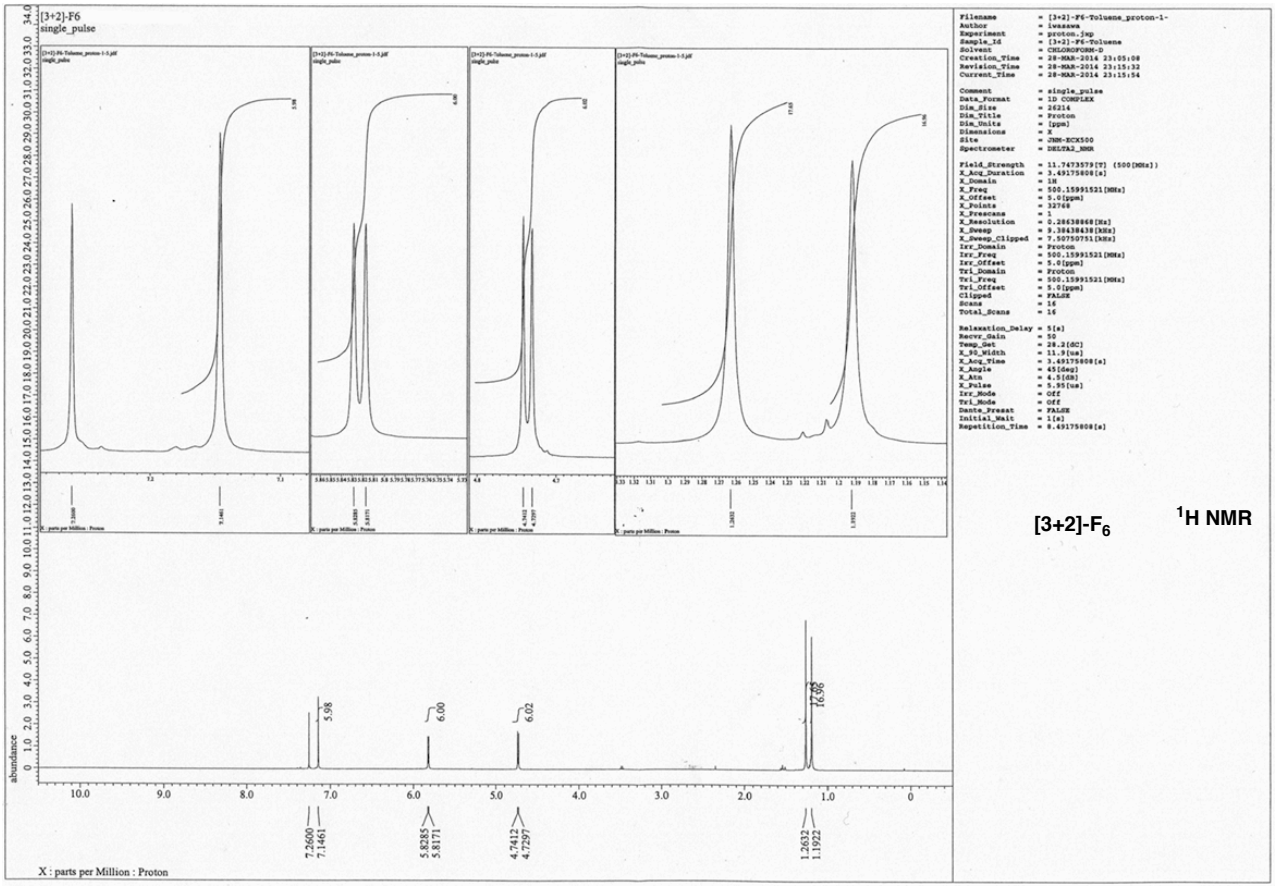
2,4,6-Trifluoro-1,3,5-benzenetriboronic acid tris(pinacol) ester **2** (27.2 mg, 53 mmol) was added to a solution of *rac*-tetrol **1** (20.8 mg, 75 mmol) in methanol/*o*-xylene (3.5 mL/0.1 mL). After the mixture was stirred at room temperature for 24 h, *o*-xylene@*homo*-**[3+2]-F_6** was obtained as a white powder by filtration (25.6 mg, 20 mmol, 82%).

o-xylene@*homo*-**[3+2]-F_6**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 6H), 5.92 (d, J = 5.5 Hz, 6H), 5.50 (dd, J = 5.5, 3.5 Hz, 2H), 4.72 (d, J = 5.5 Hz, 6H), 3.82 (dd, J = 5.5, 3.5 Hz, 2H), 1.56 (s, 18H), 1.18 (s, 18H), 0.34 (s, 6H).

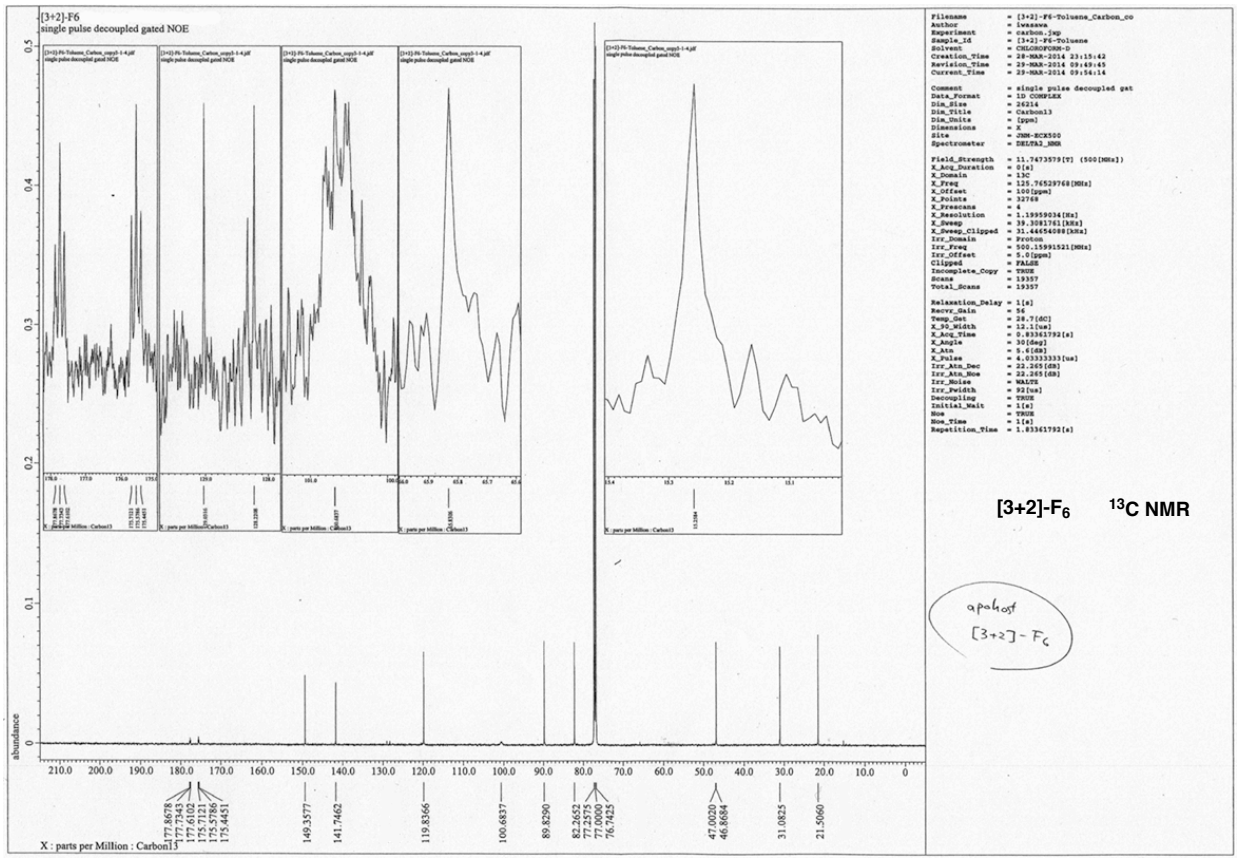


apohost *homo*-**[3+2]-F_6**: *o*-xylene@**[3+2]-F_6** was suspended in Et_2O and the mixture was sonicated. White precipitate was collected by filtration and dried under vacuum to give the desired apohost.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (s, 6H), 5.82 (d, J = 5.7 Hz, 6H), 4.74 (d, J = 5.7 Hz, 6H), 1.26 (s, 18H), 1.19 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7 (dt, J = 269, 16.7 Hz), 149.4, 141.7, 119.8, 100.7, 89.8, 82.3, 46.9, 31.1, 21.5; ^{11}B NMR (127 MHz, $CDCl_3$): δ 29.2; IR (ATR): 2955, 1594, 1364, 1341, 1308, 1280, 1256, 1159, 1119, 1018, 999, 877, 832, 795, 705, 658, 619 cm^{-1}; HR-MS (FAB, *m/z*) $[M]^+$ calcd. for $C_{60}H_{54}B_6F_6O_{12}$, 1145.4114; found,1145.4064.



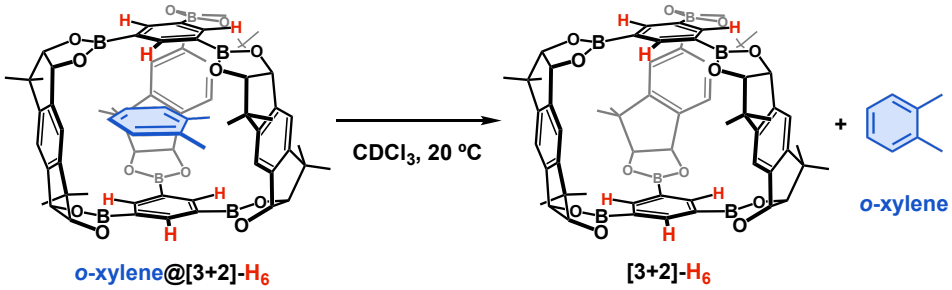
[3+2]-F$_6$ **^{1}H NMR**



[3+2]-F$_6$ **^{13}C NMR**

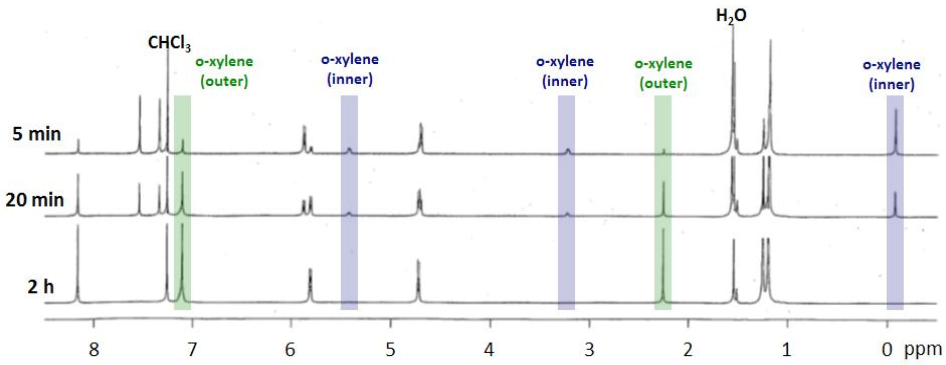
4. Kinetic study

Guest-release of *o*-xylene@*homo*-**[3+2]-H$_6$**



o-xylene@*homo*-**[3+2]-H$_6$** (1.2 mg, 1.0 μmol) was placed in an NMR tube and dissolved in $CDCl_3$ (0.5 mL) at −60 °C. ^{1}H NMR spectra of the mixture was recorded at 20 °C periodically.

(a)



(b)

homo-[3+2]-H6	20°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.858	1.0000
300	1.654	0.8902
600	1.469	0.7906
900	1.338	0.7201
1200	1.16	0.6243
1500	1.05	0.5651

(c)

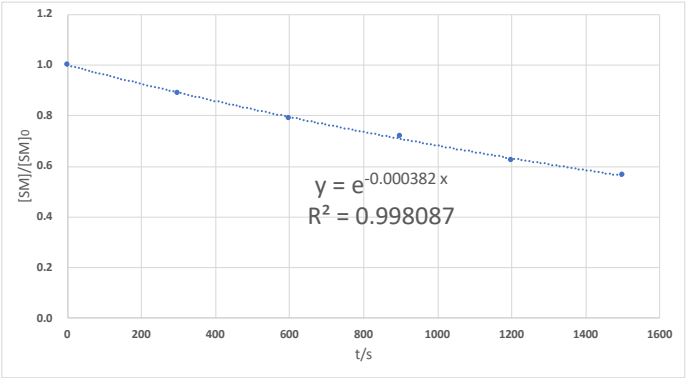
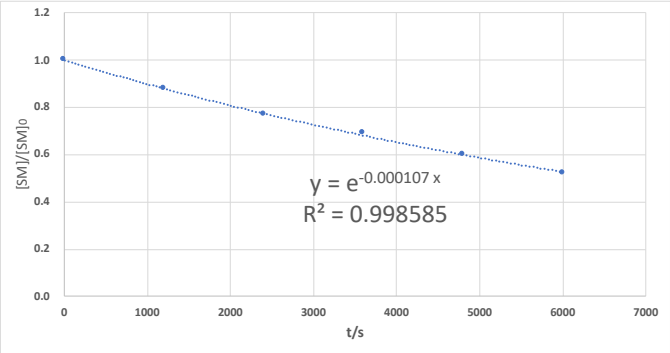


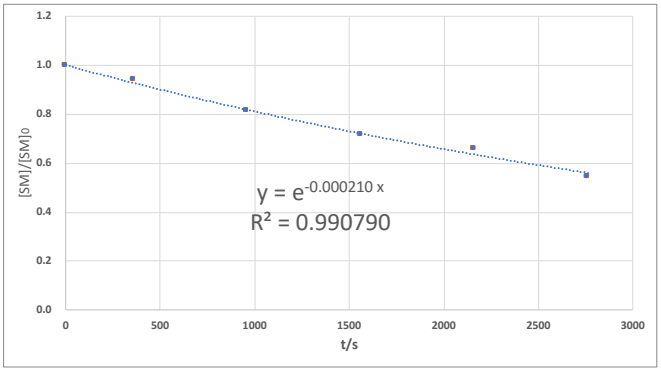
Fig. S1 Guest-release of *o*-xylene@*homo*-[3+2]-H$_6$ at 20 °C. (a) Time-dependent ^{1}H NMR spectra (t = 5 min, 20 min, 2 h) (b) Table of time dependence of concentration of *o*-xylene@**[3+2]-H$_6$** (c) First-order plot (k = 3.82 × 10^{-4} s^{-1}).

Similar examinations were carried out at various temperatures in order to determine activation parameters of the guest-release by Arrhenius plot.

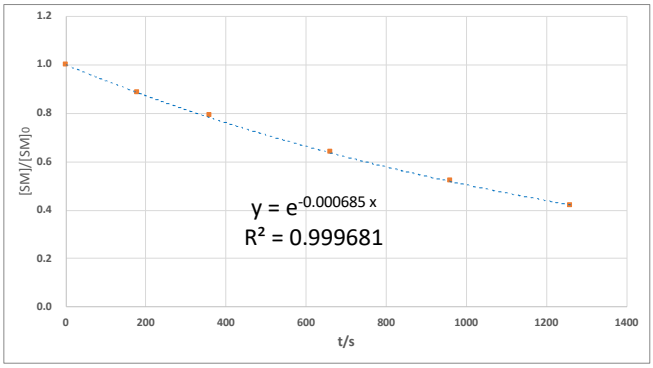
homo-[3+2]-H6	10°C	
t/s	[SM]/mM	[SM]/[SM]0
0	2.009	1.0000
1200	1.765	0.8785
2400	1.544	0.7685
3600	1.391	0.6924
4800	1.207	0.6008
6000	1.05	0.5226



homo-[3+2]-H6	15°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.953	1.0000
360	1.842	0.9432
960	1.591	0.8146
1560	1.4	0.7168
2160	1.288	0.6595
2760	1.066	0.5458



homo-[3+2]-H6	25°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.694	1.0000
180	1.5	0.8855
360	1.338	0.7898
660	1.082	0.6387
960	0.879	0.5189
1260	0.71	0.4191



homo-[3+2]-H6	30°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.628	1.0000
180	1.346	0.8268
360	1.071	0.6579
540	0.882	0.5418
720	0.68	0.4177
900	0.577	0.3544
1080	0.466	0.2862

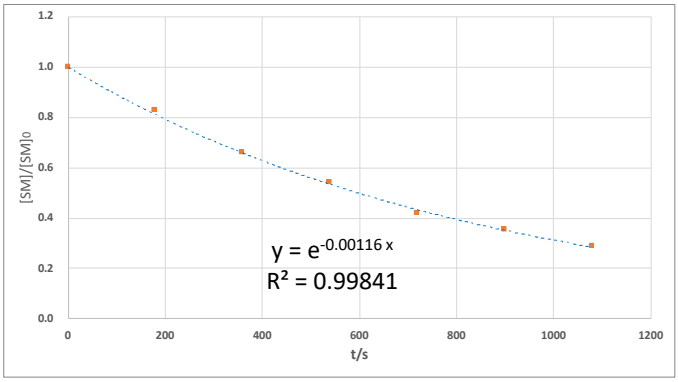


Fig. S2 Guest-release of *o*-xylene@*homo*-[3+2]-H$_6$ at various temperatures.

homo-[3+2]-H6	Arrhenius Plot
T−1/K−1	*k*
0.003289	0.00116
0.003341	0.000685
0.003394	0.000382
0.00345	0.00021
0.003507	0.000107

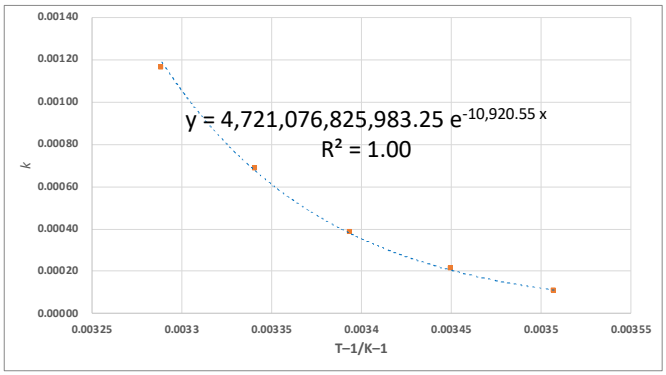


Fig. S3 Arrhenius plot of guest-release of *o*-xylene@*homo*-[3+2]-H$_6$.

(at 20 °C)

$E_a = 10920.55R$ J mol^{-1} = 90.793 kJ mol^{-1} = 21.7 kcal mol^{-1}

$\ln (k/T) = -(\Delta H^{\ddagger}/R)(1/T) + \ln (k_B/h) + (\Delta S^{\ddagger}/R)$

$\Delta H^{\ddagger} = -10607R$ J mol^{-1}= 21.1 kcal mol^{-1}

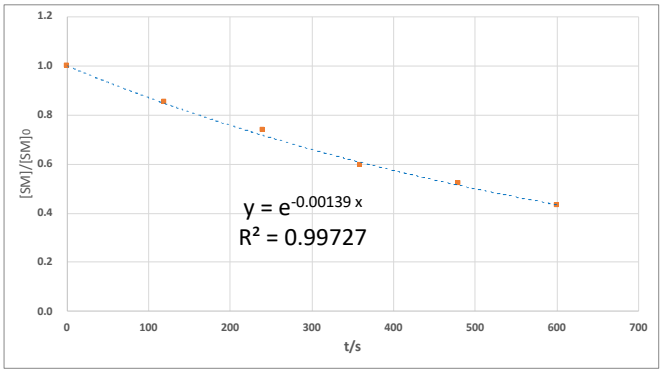
$\Delta S^{\ddagger} = R(22.44-23.759) = -2.6$ cal mol^{-1} K^{-1}

$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} = 21.9$ kcal mol^{-1}

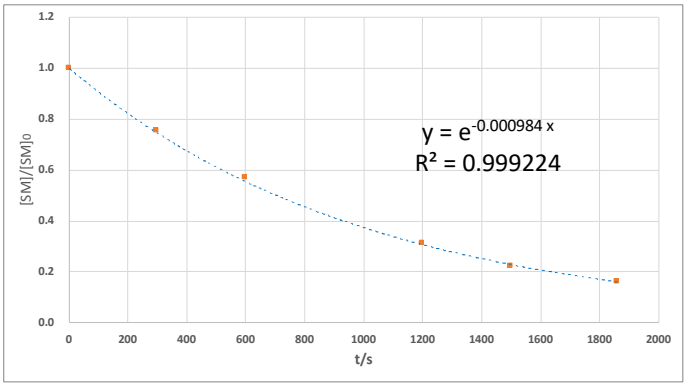
(R: gas constant, h: Planck constant, k_B: Boltzmann constant)

Guest-release of *o*-xylene@*homo*-**[3+2]-H$_6$** in the presence of additive

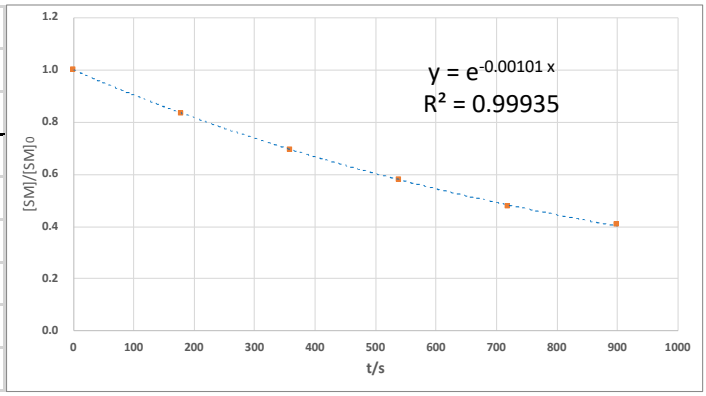
homo-[3+2]-H6	+ DABCO	
t/s	[SM]/mM	[SM]/[SM]0
0	0.9856	1.0000
120	0.8384	0.8506
240	0.7255	0.7361
360	0.5856	0.5942
480	0.5118	0.5193
600	0.4251	0.4313



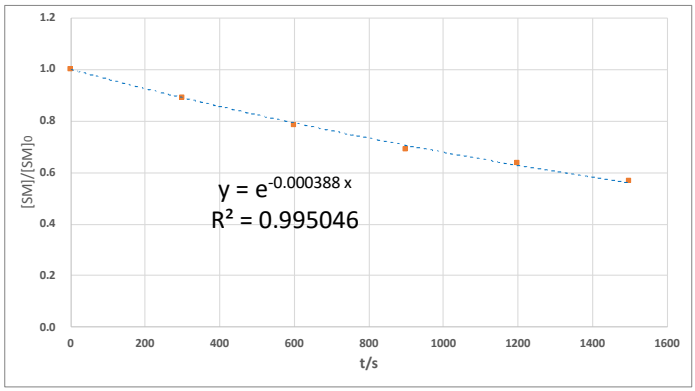
homo-[3+2]-H6	+ DMAP	
t/s	[SM]/mM	[SM]/[SM]0
0	1.098	1.0000
300	0.8292	0.7552
600	0.6244	0.5687
1200	0.3411	0.3107
1500	0.2434	0.2217
1860	0.1775	0.1617



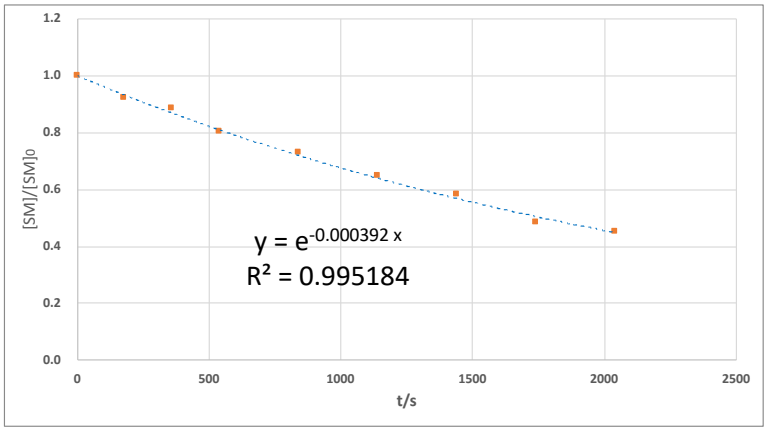
homo-[3+2]-H6	+ piperidine	
t/s	[SM]/mM	[SM]/[SM]0
0	0.9896	1.0000
180	0.8225	0.8311
360	0.6859	0.6931
540	0.5706	0.5766
720	0.4715	0.4765
900	0.4034	0.4076



homo-[3+2]-H6	+ methanol	
t/s	[SM]/mM	[SM]/[SM]0
0	1.408	1.0000
300	1.249	0.8871
600	1.104	0.7841
900	0.9668	0.6866
1200	0.8928	0.6341
1500	0.7977	0.5665



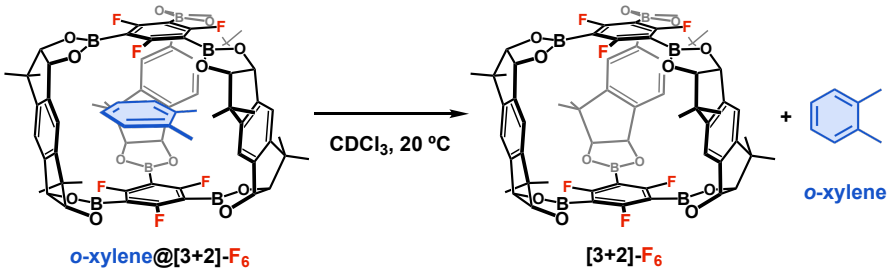
homo-[3+2]-H6	+ TMP	
t/s	[SM]/mM	[SM]/[SM]0
0	1.522	1.0000
180	1.4	0.9198
360	1.346	0.8844
540	1.221	0.8022
840	1.111	0.7300
1140	0.9859	0.6478
1440	0.8861	0.5822
1740	0.7394	0.4858
2040	0.6863	0.4509



(TMP = 2,2,6,6-Tetramethylpiperidine)

Fig. S4 Guest-release of *o*-xylene@*homo*-[3+2]-H$_6$ in the presence of various additives at 20 °C.

Guest-release of *o*-xylene@*homo*-**[3+2]-F$_6$**



o-xylene@*homo*-**[3+2]-F$_6$** (1.2 mg, 10 mmol) was placed in an NMR tube and dissolved in $CDCl_3$ (0.5 mL) at room temperature. ^{1}H NMR spectra of the mixture was recorded at 20 ºC periodically.

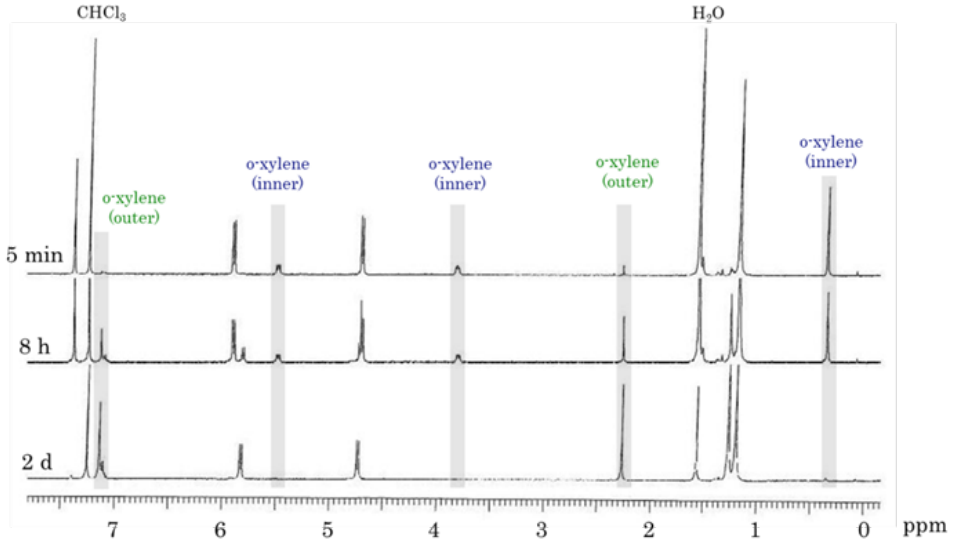
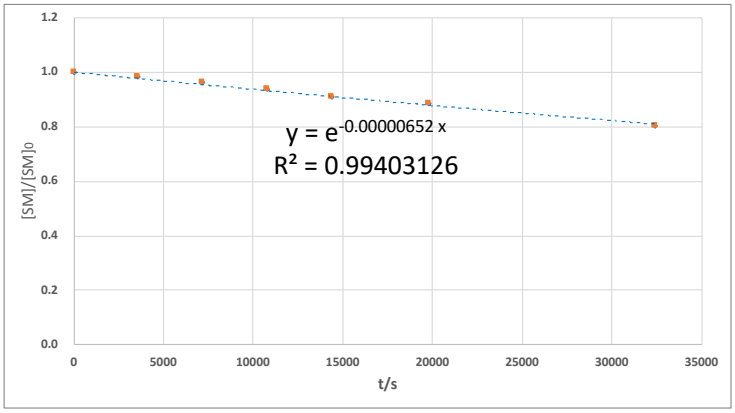
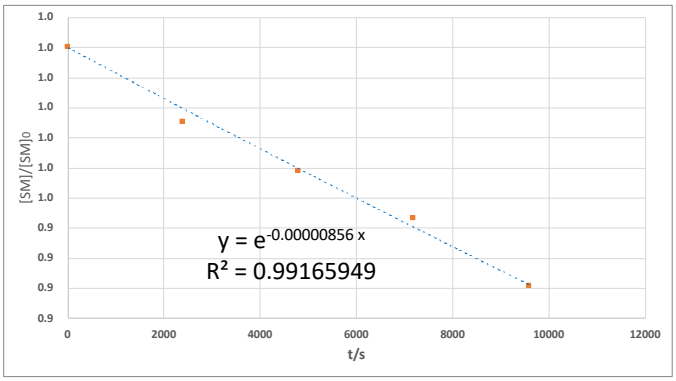


Fig. S5 Guest-release of *o*-xylene@*homo*-[3+2]-F$_6$ at 20 °C. Time-dependent ^{1}H NMR spectra (t = 5 min, 8 h, 2 d).

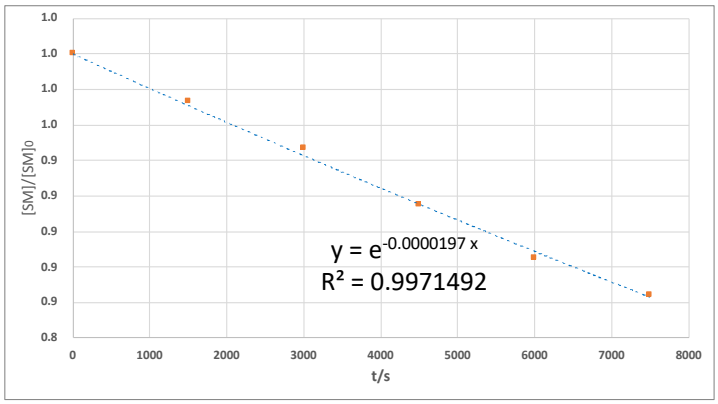
homo-[3+2]-F6	20°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.837	1.0000
3600	1.802	0.9809
7200	1.765	0.9608
10800	1.724	0.9385
14400	1.673	0.9107
19800	1.623	0.8835
32400	1.476	0.8035



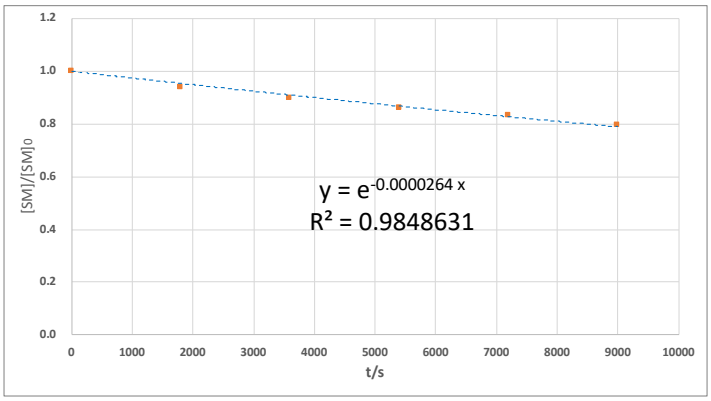
homo-[3+2]-F6	25°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.724	1.0000
2400	1.681	0.9751
4800	1.653	0.9588
7200	1.626	0.9432
9600	1.587	0.9205



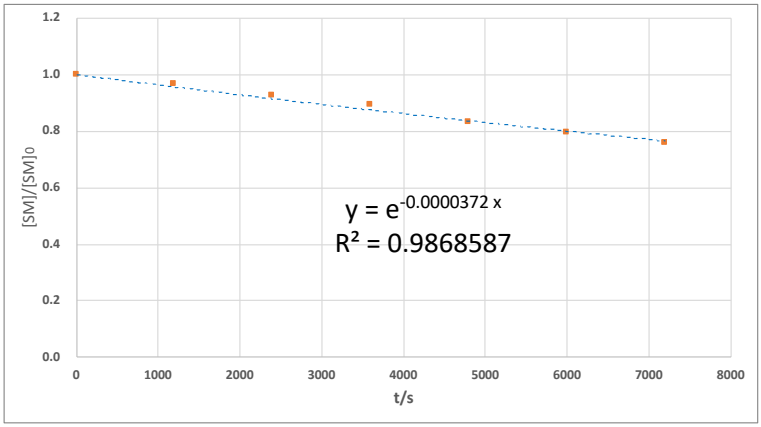
homo-[3+2]-F6	30°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.852	1.0000
1500	1.802	0.9730
3000	1.754	0.9471
4500	1.695	0.9152
6000	1.639	0.8850
7500	1.6	0.8639



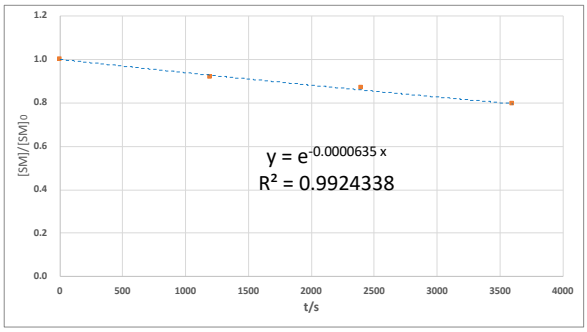
homo-[3+2]-F6	35°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.613	1.0000
1800	1.515	0.9392
3600	1.449	0.8983
5400	1.389	0.8611
7200	1.342	0.8320
9000	1.282	0.7948



homo-[3+2]-F6	40°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.833	1.0000
1200	1.77	0.9656
2400	1.695	0.9247
3600	1.639	0.8942
4800	1.527	0.8331
6000	1.46	0.7965
7200	1.389	0.7578



homo-[3+2]-F6	45°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.802	1.0000
1200	1.653	0.9173
2400	1.563	0.8674
3600	1.429	0.7930



homo-[3+2]-F6	50°C	
t/s	[SM]/mM	[SM]/[SM]0
0	1.754	1.0000
600	1.6	0.9122
1200	1.515	0.8637
1800	1.389	0.7919
2400	1.333	0.7600
3000	1.299	0.7406
3600	1.19	0.6784

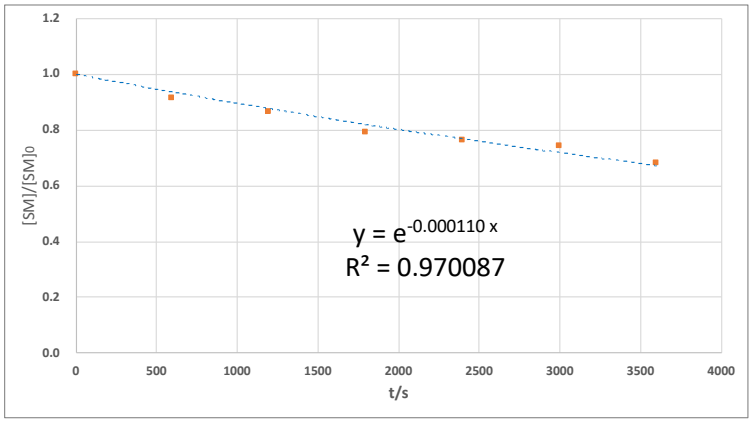


Fig. S6 Guest-release of *o*-xylene@*homo*-[3+2]-F_6 at various temperatures.

homo-[3+2]-F6	Arrhenius Plot
T−1/K−1	*k*
0.003411	0.00000652
0.003354	0.00000856
0.003299	0.0000197
0.003245	0.0000264
0.003193	0.0000372
0.003143	0.0000635
0.003095	0.00011

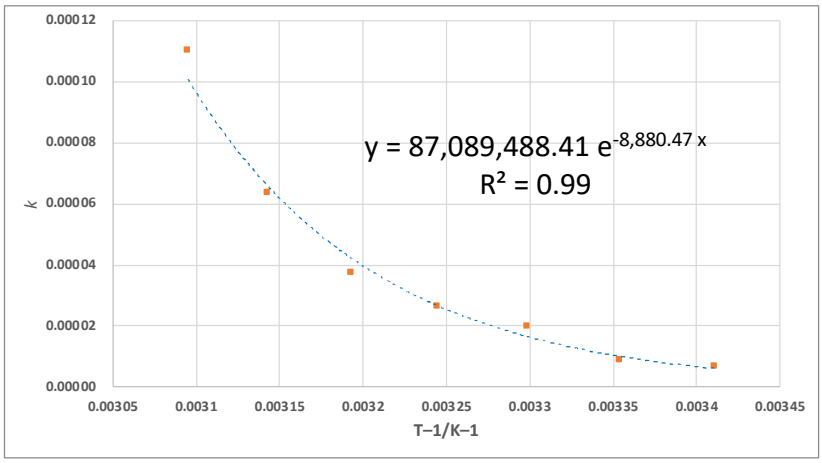


Fig. S7 Arrhenius plot of guest-release of *o*-xylene@*homo*-[3+2]-F_6.

(at 20 °C)

$E_a = 8880.47R$ J mol^{-1} = 73.832 kJ mol^{-1} = 17.6 kcal mol^{-1}

$\ln (k/T) = -(\Delta H^{\ddagger}/R)(1/T) + \ln (k_B/h) + (\Delta S^{\ddagger}/R)$

$\Delta H^{\ddagger} = -8573.2R$ J mol^{-1}= 17.0 kcal mol^{-1}

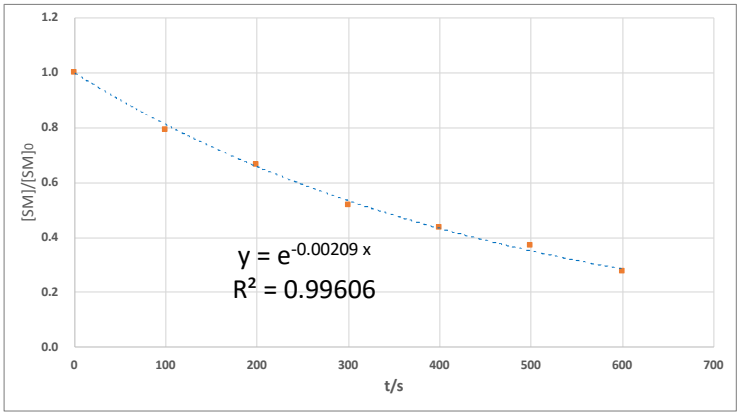
$\Delta S^{\ddagger} = R(11.56-23.759) = -24.2$ cal mol^{-1} K^{-1}

$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} = 24.1$ kcal mol^{-1}

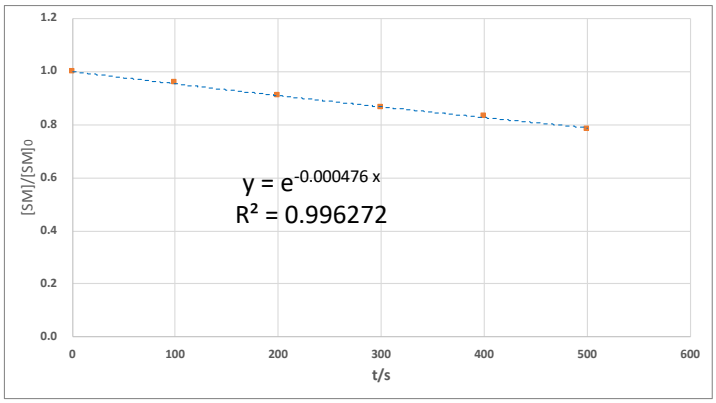
(R: gas constant, h: Planck constant, k_B: Boltzmann constant)

Guest-release of *o*-xylene@*homo*-**[3+2]-F$_6$** in the presence of additive

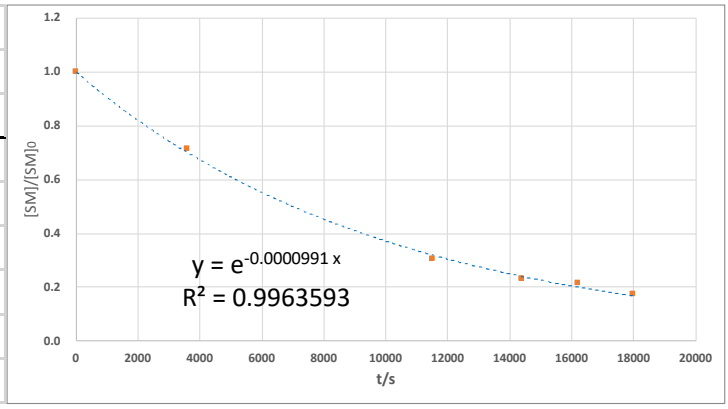
homo-[3+2]-F6	+ DMAP	
t/s	[SM]/mM	[SM]/[SM]0
0	1.266	1.0000
100	1	0.7899
200	0.8403	0.6637
300	0.6557	0.5179
400	0.5525	0.4364
500	0.4662	0.3682
600	0.3509	0.2772



homo-[3+2]-F6	+ DABCO	
t/s	[SM]/mM	[SM]/[SM]0
0	1.667	1.0000
100	1.6	0.9598
200	1.515	0.9088
300	1.439	0.8632
400	1.389	0.8332
500	1.307	0.7840



homo-[3+2]-F6	+ methanol	
t/s	[SM]/mM	[SM]/[SM]0
0	1.736	1.0000
3600	1.235	0.7114
11520	0.5249	0.3024
14400	0.3968	0.2286
16200	0.369	0.2126
18000	0.2981	0.1717



homo-[3+2]-F6	+ TMP	
t/s	[SM]/mM	[SM]/[SM]0
0	1.818	1.0000
2160	1.626	0.8944
3240	1.575	0.8663
6720	1.342	0.7382
10800	1.13	0.6216

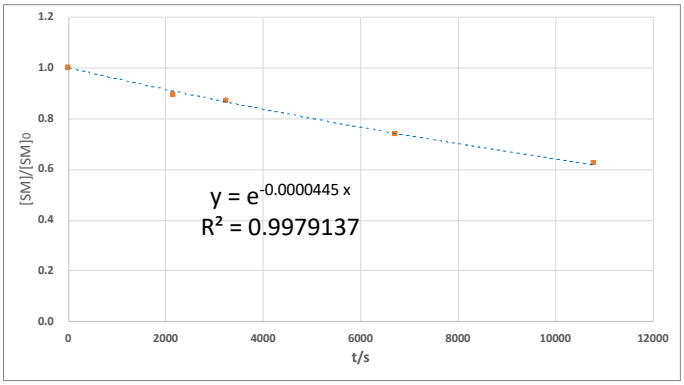
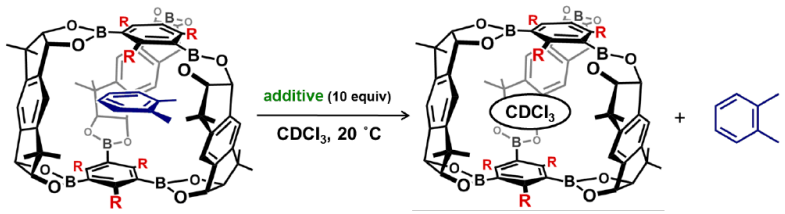


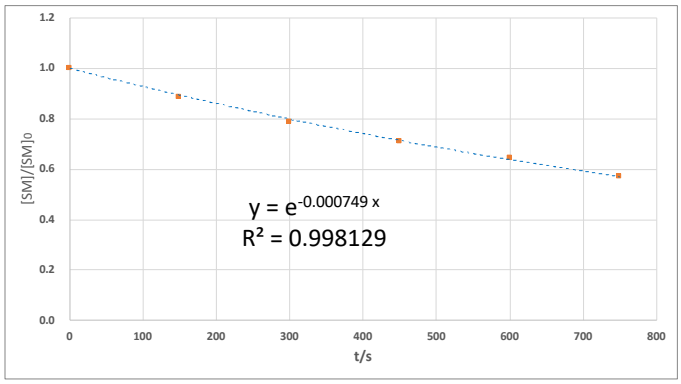
Table S1 Acceleration effect of additives



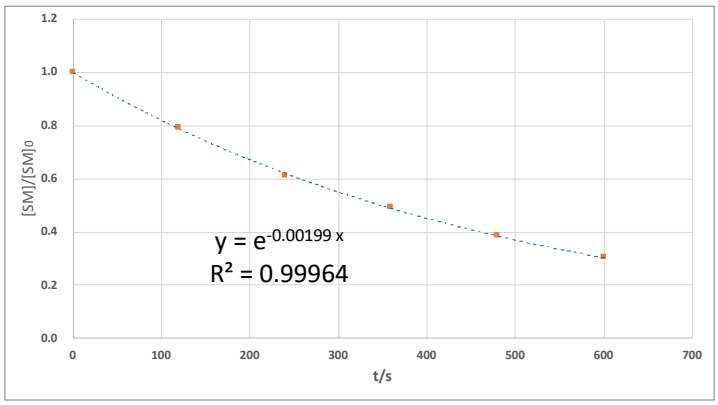
additive	none	MeOH				
R = H	3.82×10^{-4} (1.0)	3.88×10^{-4} (1.0)	1.39×10^{-3} (3.6)	9.84×10^{-4} (2.6)	1.01×10^{-3} (2.6)	3.92×10^{-4} (1.0)
F	6.52×10^{-6} (1.0)	9.91×10^{-6} (1.5)	4.76×10^{-4} (73)	2.09×10^{-3} (320)	5 min complete (>1840)	4.45×10^{-5} (6.8)

Effect of DMAP concentration to the guest-release of *o*-xylene@*homo*-**[3+2]-F$_6$**

homo-[3+2]-F6	7.37 mM	
t/s	[SM]/mM	[SM]/[SM]0
0	1.56	1.0000
150	1	0.8840
300	1.23	0.7885
450	1.108	0.7103
600	1.004	0.6436
750	0.8919	0.5717



homo-[3+2]-F6	14.7 mM	
t/s	[SM]/mM	[SM]/[SM]0
0	1.405	1.0000
120	1	0.7907
240	0.8569	0.6099
360	0.6895	0.4907
480	0.5437	0.3870
600	0.4248	0.3023



homo-[3+2]-F6	36.8 mM	
t/s	[SM]/mM	[SM]/[SM]0
0	1.053	1.0000
120	0.623	0.5916
240	0.3802	0.3611
360	0.2018	0.1916
480	0.0985	0.0935

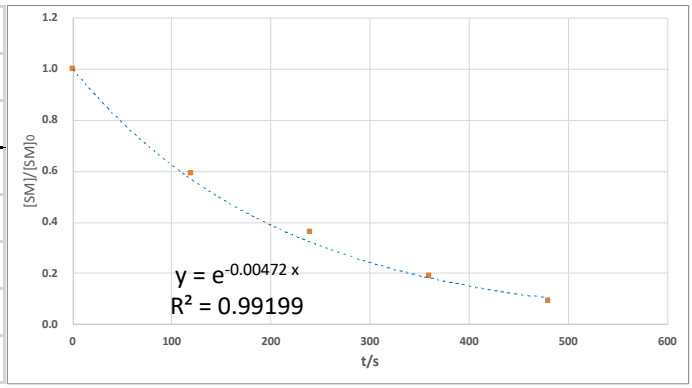


Fig. S8 Effect of DMAP concentration to the guest-release of *o*-xylene@*homo*-[3+2]-F$_6$

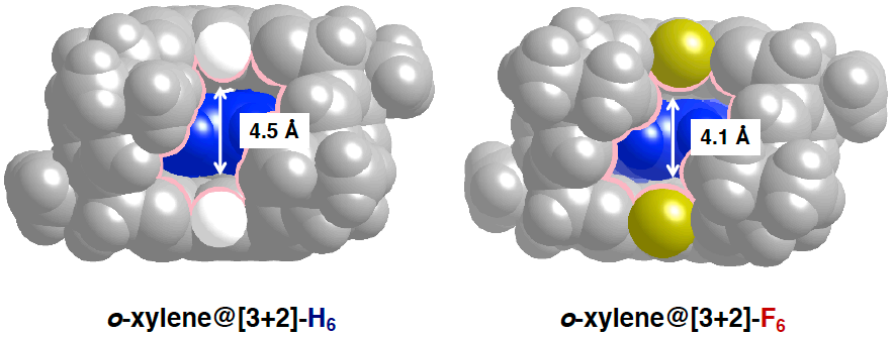


Fig. S9 Side views of X-ray structures of *o*-xylene@[3+2]-H_6 and *o*-xylene@[3+2]-F_6.

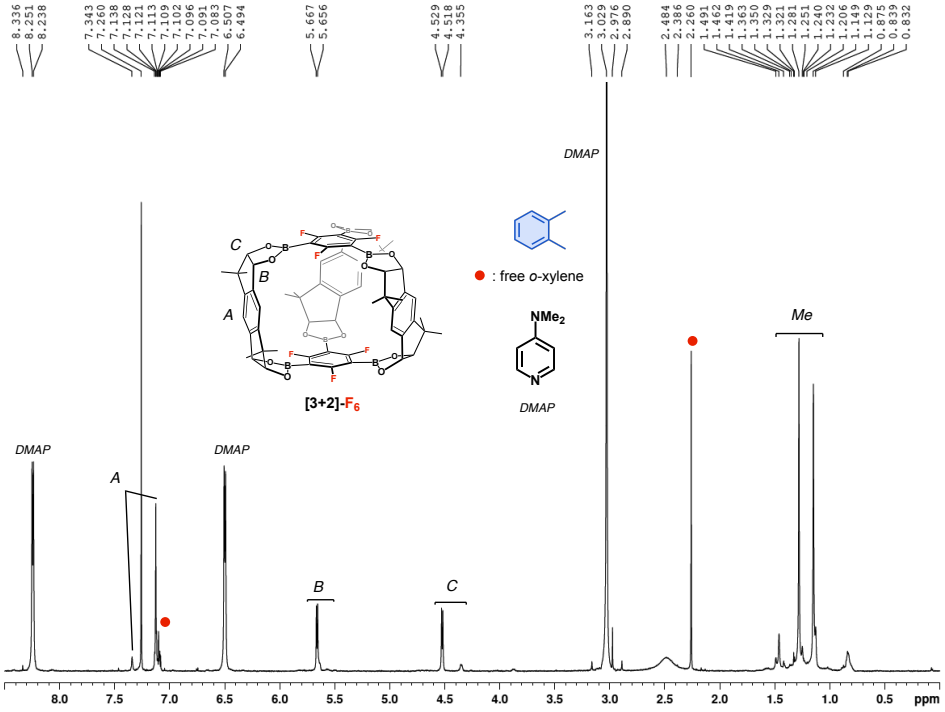


Fig. S10 ^{1}H NMR spectrum (500 MHz, 300 K) of a $CDCl_3$ solution of *o*-xylene@*homo*-[3+2]-F_6 30 min after the addition of DMAP (10 equivalents).

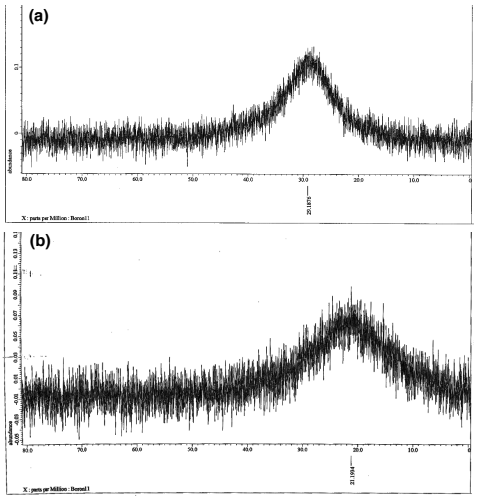


Fig. S11 ^{11}B NMR spectra (160 MHz, 300 K) of (a) *homo*-[3+2]-F_6 and (b) *homo*-[3+2]-F_6+DMAP (10 equivalents).

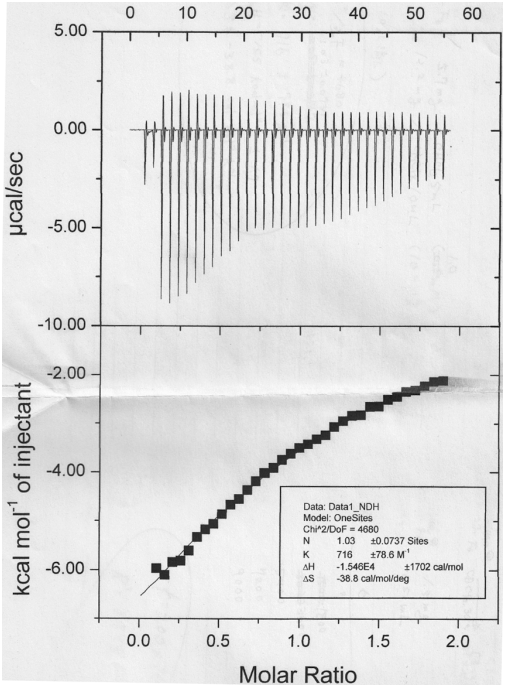
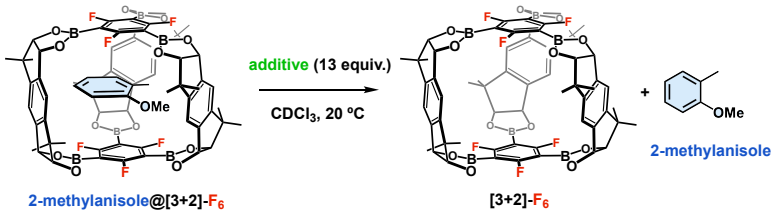


Fig. S12 ITC analysis (25 ºC) of *homo*-[3+2]-F_6 with DMAP.

Association constant K = 716 (M^{-1})

Table S2 Acceleration effect of additives in the case of 2-methylanisole@[3+2]-F_6



additive	none	
	5.64×10^{-5} (1.0)	5 min complete (> 213)

2-methylanisole@**[3+2]-F_6** was obtained by similar procedure by using 2-methyanisole instead of *o*-xylene. Stimuli-responsive guest-release was also observed by using DMAP (13 equiv.) as additive (Table S2, Fig. S13, 14).

2-methylanisole		
homo-[3+2]-F6	20°C	
t/s	[SM]/mM	[SM]/[SM]0
0	2	1.0000
3600	1.6	0.8000
7200	1.299	0.6494
10800	1.526	0.5263
14400	0.847	0.4237
19800	0.699	0.3497

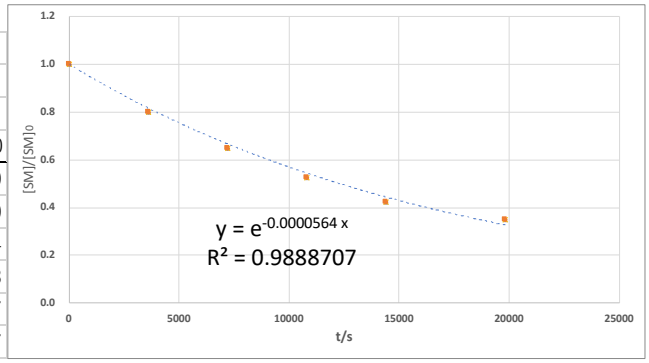


Fig. S13 Guest-release of 2-methylanisole@*homo*-[3+2]-F_6.

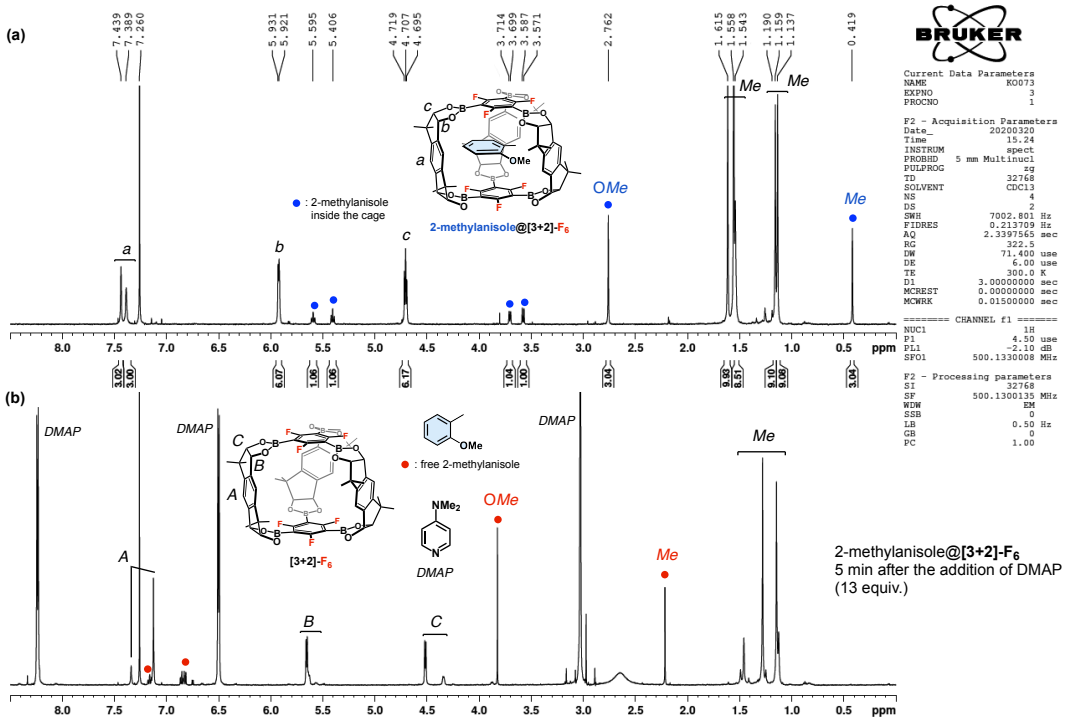


Fig. S14 ^{1}H NMR spectrum of (a) 2methylanisole@[3+2]-F_6 and (b) 5 min after the addition of DMAP (13 equiv.).

5. X-ray crystallographic analysis of *o*-xylene@*homo*-[3+2]-F_6

The single crystal of *o*-xylene@*homo*-**[3+2]-F_6** suitable for X-ray crystallographic analysis was obtained by slow cooling of hot *o*-xylene solution of *homo*-**[3+2]-F_6**. Because of highly disordered guest molecules, residual densities remain around the guest molecules and some A and B level alerts remains. The responses of A and B alerts were described below.

_vrf_DIFMN02_global

;

Because of highly disordered guest molecules (*o*-xylene), residual densities remain around the guest molecules.

;

_vrf_PLAT097_global

;

Because of highly disordered guest molecules (o-xylene), residual densities remain around the guest molecules.

;

_vrf_PLAT098_global

;

Because of highly disordered guest molecules (*o*-xylene), residual densities remain around the guest molecules.

;

_vrf_PLAT934_global

;

Because of highly disordered guest molecules (*o*-xylene), some reflections did not match between observation and calculations.

;

_vrf_PLAT043_global

;

Hydrogen atoms of *o*-xylene molecules are not considered in the refinements, because *o*-xylene molecules are highly disordered. This caused the calculated and reported molecular weight difference.

;

_vrf_PLAT084_global

;

Because of highly disordered guest molecules (*o*-xylene), R-factors are somewhat high.

;

_vrf_PLAT315_global

;

Hydrogen atoms of *o*-xylene molecules are not considered in the refinements, because *o*-xylene molecules are highly disordered.

;

_vrf_PLAT972_global

;

Because of highly disordered guest molecules (*o*-xylene), residual densities remain around the guest molecules.

;

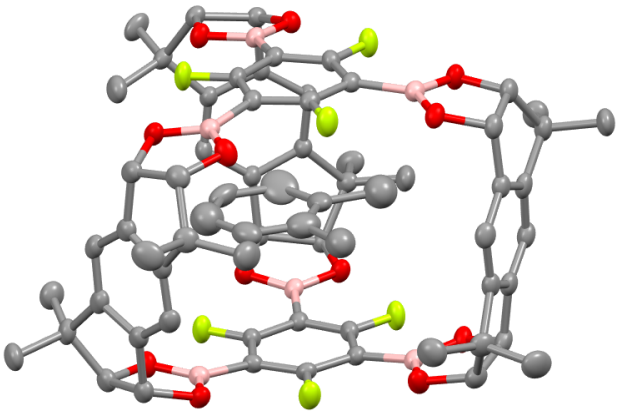


Fig. S15 Ellipsoid drawing of the crystal structure of *o*-xylene@*homo*-[3+2]-F_6 at 50% probability. All hydrogen atoms are omitted for clarity. (C = gray, O = red, B = pink, F = yellow).

Table S2 Crystal data and structure refinement for *o*-xylene@*homo*-**[3+2]-F_6**

Identification code	shelx	
Empirical formula	C_{88} H_{94} B_6 F_6 O_{12}	
Formula weight	1514.42	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	*C* 2/c	
Unit cell dimensions	*a* = 18.0660(7) Å	α = 90°.
	b = 19.9550(7) Å	*β* = 108.477(1)°.
	c = 24.1330(8) Å	*γ* = 90°.
Volume	8251.6(5) Å^3	
Z	4	
Density (calculated)	1.219 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	3176	
Crystal size	0.20 x 0.20 x 0.20 mm^3	
Theta range for data collection	3.05 to 27.42°.	
Index ranges	-23<=h<=23, -25<=k<=25, -28<=l<=31	
Reflections collected	39870	
Independent reflections	9398 [R(int) = 0.0237]	
Completeness to theta = 25.24°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9827 and 0.9827	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	39870 / 23 / 460	
Goodness-of-fit on F^2	1.931	
Final R indices [I>2sigma(I)]	R_1 = 0.1295, wR_2 = 0.4076	
R indices (all data)	R_1 = 0.1456, wR_2 = 0.4332	
Largest diff. peak and hole	2.253 and -2.782 e.Å^{-3}	

6. References

S1 H. Takahagi, S. Fujibe and N. Iwasawa, *Chem. – Eur. J.* 2009, **15**, 13327–13330.

S2 H. Sakurai, N. Iwasawa and K. Narasaka, *Bull. Chem. Soc. Jpn.* 1996, **69**, 2585–2594.