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Stabilization of liquid active guests via nanoconfinement into a flexible microporous Metal-Organic Framework.

Paolo P. Mazzeo[a,b], Davide Balestri[a], Alessia Bacchi[a,b], Paolo Pelagatti[a,c]

a Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università di Parma, Parco Area delle Scienze 17/A, 43124 Parma (Italy)

b Biopharmanet-TEC, Università di Parma, Parco Area delle Scienze 27/A, 43124 Parma (Italy)

c Centro Interuniversitario di Reattività Chimica e Catalisi (CIRCC), Via Celso Ulpiani 27, 70126 Bari (Italy)

Supplementary information

11 pages

1. Synthetic procedures

Synthesis of the ligand (N,N'-(1,1'-biphenyl)-4,4'-diylbis-4-pyridinecarboxamide, (bpba))

An oven dried 100 mL Schlenk flask was charged with 4,4′-dibromobiphenyl (356 mg, 1.14 mmol), isonicotinamide (334 mg, 2.73 mmol, 2.4 equivalents), K_2CO_3 (441 mg, 3.18 mmol, 2.8 equivalents) and BrettPhos Pd G1® catalyst (10 mg, 0.01 mmol, 1 mol%). The vessel was evacuated and backfilled with nitrogen 3 times, then tert-butanol (24 mL) was added. The resulting reaction mixture was stirred overnight at 110°C. Bpba was isolated by centrifugation and washed with water (3 x 15 mL), to provide an off-white solid with high purity (439 mg, 1.11mmol, 98%).

Mp: 382 °C; 1H-NMR (400 MHz, DMSO-d, 25 °C): δ 10.60 (bs, NH, 2H), 8.80 (d, CHPyr, J=5.8 Hz, 4H), 7.90-7.86 (m, CHPyr + CHAr, 8H), 7.72 (d, CHAr, J= 8.7 Hz, 4H) ppm; 13C{1H}-NMR (100.77 MHz, DMSO-d, 25 °C): δ 164.4, 150.7, 142.4, 138.3, 135.7, 127.1, 122.1, 121.3 ppm; IR (ATR, cm-1): 3334 (NH), 1647 (C=O), 1611, 1587, 1552, 1507, 1409, 1397, 1337, 1318, 1286, 1258, 1218, 1065, 1004, 991, 904, 814, 754, 710, 665, 650, 581; MS (DEP/EI(+)): Calculated for [M]+ $[C_{24}H_{18}N_4O_2]$+ m/z= 394.14, found m/z= 394.2.

PUM168 synthesis

In a 70 mL pyrex glass tube, bpba (0.2 mmol, 80 mg) and biphenyl-4,4'-dicarboxylic acid (0.4 mmol, 96 mg) and $Zn(NO_3)_2 \cdot 6H_2O$ (0.4 mmol, 120 mg) were added to 41 mL of dimethylformamide (DMF). The resulting mixture was sonicated and heated at 80°C. After 1 week the reaction vessel was slowly cooled to room temperature. The resulting large yellow block crystals were washed with DMF (2 x 10mL) and stored in fresh DMF before further analysis. IR (ATR, cm-1): 1654, 1636, 1604, 1526, 1498, 1384, 1321, 1289, 1255, 1176, 1091, 1065, 1034, 1005, 856, 840, 826, 769, 701, 680, 659, 580.

Soaking Experiments

Size selected crystals of approximately 150 x 150 x 100 µm of native PUM168 (approximately 5 mg) were transferred into a 5 mL glass vial and dipped into neat propofol, carvacrol or menthone (0.5 to 1.0 mL). The vial was closed, and crystals soaked at room temperature for the desired time, (approx. 7 days) by means of a rocking shaker. For NMR and TGA samples, loaded crystals were separated from the soaking liquid by fishing them with a spatula and quickly dried on filter paper. Activation of the crystals, as usually done for adsorption purposes wit MOF materials, was avoided to preserve intact the starting framework.

2. X-ray Crystallography

Table SI1: **Crystallographic information.** Crystal structures have been deposited at the Cambridge Crystallographic Data Center with deposition codes: CCDC 2094688-2094690.

Identification code	**PUM168@propofol**	**PUM168@carvacrol**	**PUM168@mentone**
Empirical formula	$C_{126.62}H_{125.75}N_{7.62}O_{20.25}Zn_3$	$C_{130.35}H_{132.3}N_{8.95}O_{22.3}Zn_3$	$C_{94}H_{83}N_8O_{18}Zn_3$
Formula weight	2274.45	2377.15	1805.03
Temperature/K	100	100	100
Crystal system	triclinic	triclinic	triclinic
Space group	P-1	P-1	P-1
a/Å	15.263(3)	21.473(5)	15.186(3)
b/Å	30.497(6)	21.5530(9)	15.210(3)
c/Å	26.950(5)	26.886(2)	26.964(5)
α/°	89.20(3)	94.896(3)	91.53(3)
β/°	82.16(3)	102.406(8)	102.04(3)
γ/°	87.80(3)	89.986(14)	91.69(3)
Volume/Å^3	12417(4)	12106(3)	6085(2)
Z	4	4	2
ρ_{calc}g/cm^3	1.217	1.304	0.987
μ/mm^{-1}	0.618	0.638	0.615
F(000)	4764.0	4982.0	1874.0
Crystal size/mm^3	0.1 × 0.07 × 0.06	0.100 × 0.080 × 0.050	0.11 × 0.08 × 0.06
Radiation/Å	synchrotron (λ = 0.700)	synchrotron (λ = 0.700)	synchrotron (λ = 0.700)
2Θ range for data collection/°	1.502 to 50.532	1.534 to 55.636	1.522 to 50.53
Index ranges	-18 ≤ h ≤ 18 0 ≤ k ≤ 37 -32 ≤ l ≤ 32	-28 ≤ h ≤ 27 -28 ≤ k ≤ 28 0 ≤ l ≤ 35	-18 ≤ h ≤ 18 -18 ≤ k ≤ 18 0 ≤ l ≤ 32
Reflections collected	296249	375048	140458
Independent reflections	46776 R_{int} = 0.0316 R_{sigma} = 0.0227	59226 R_{int} = 0.0281 R_{sigma} = 0.0219	22884 R_{int} = 0.0268 R_{sigma} = 0.0177
Data	46776	59226	22884
Restraints	2946	1950	1213
Parameters	3272	3874	1419
Goodness-of-fit on F^2	1.042	1.038	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0898, wR_2 = 0.2695	R_1 = 0.053 wR_2 = 0.1407	R_1 = 0.0705, wR_2 = 0.2002
Final R indexes [all data]	R_1 = 0.0918, wR_2 = 0.2716	R_1 = 0.0589 wR_2 = 0.1462	R_1 = 0.0713, wR_2 = 0.2007
Largest diff. peak/hole / e Å^{-3}	2.34/-1.43	1.28/-1.16	1.04/-0.87

2.1 Thermal Ellipsoid Plots for all structures

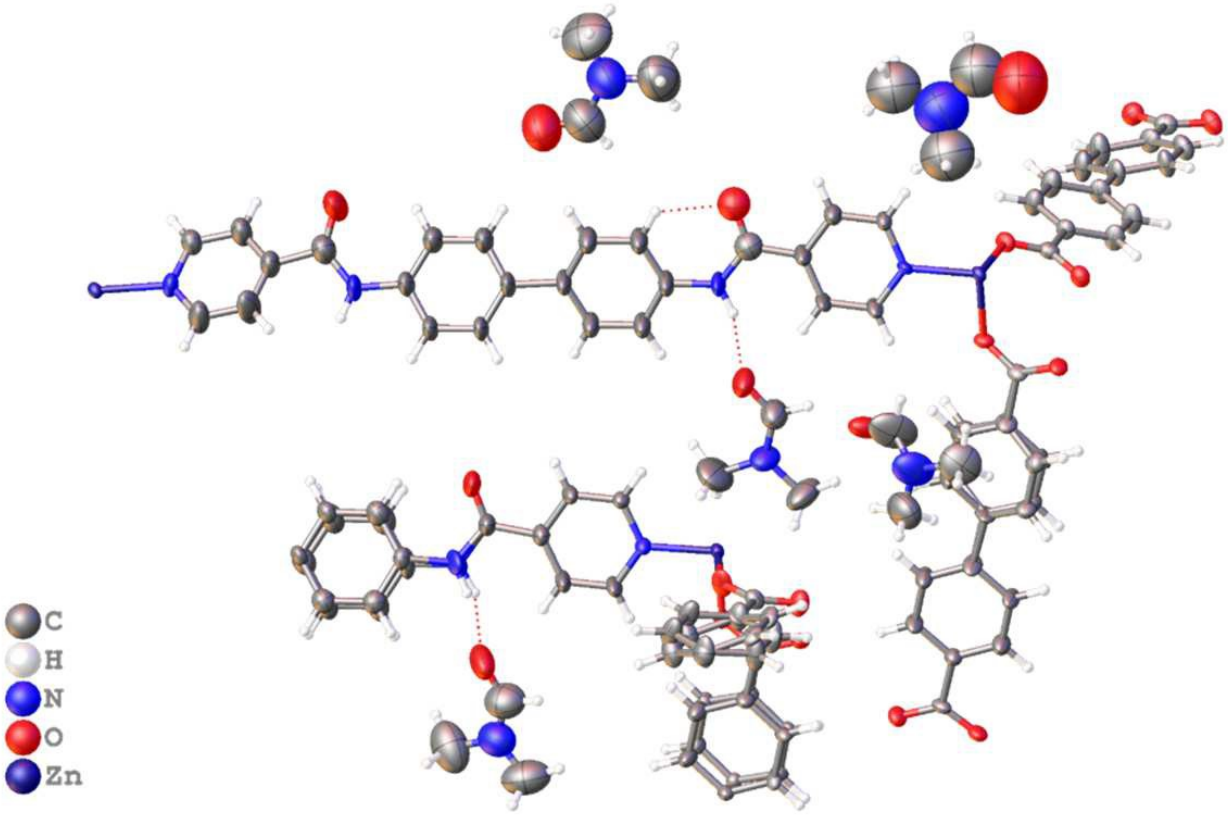

Figure SI1. The asymmetric unit of as synthesized PUM168. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity. DMF molecules are also displayed. Disorder of the nets are fully reported.

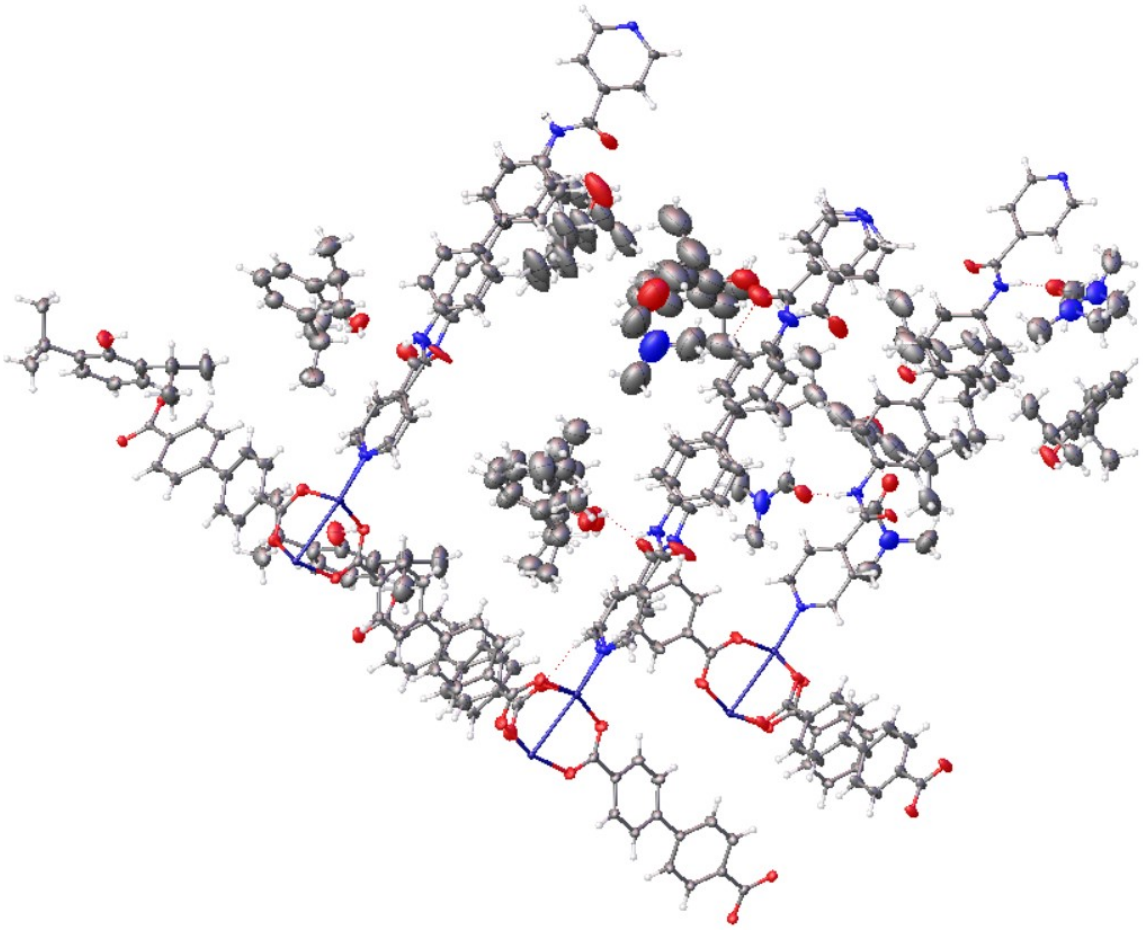

Figure SI2. The asymmetric unit of as synthesized PUM168@propofol. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity. Propofol guest molecule observed and resilient DMF molecules are also displayed. Colour code: C=grey, O=red, N=blue, H=white, Zn=purple. Disorder of the guest molecules and the a-nets are fully reported.

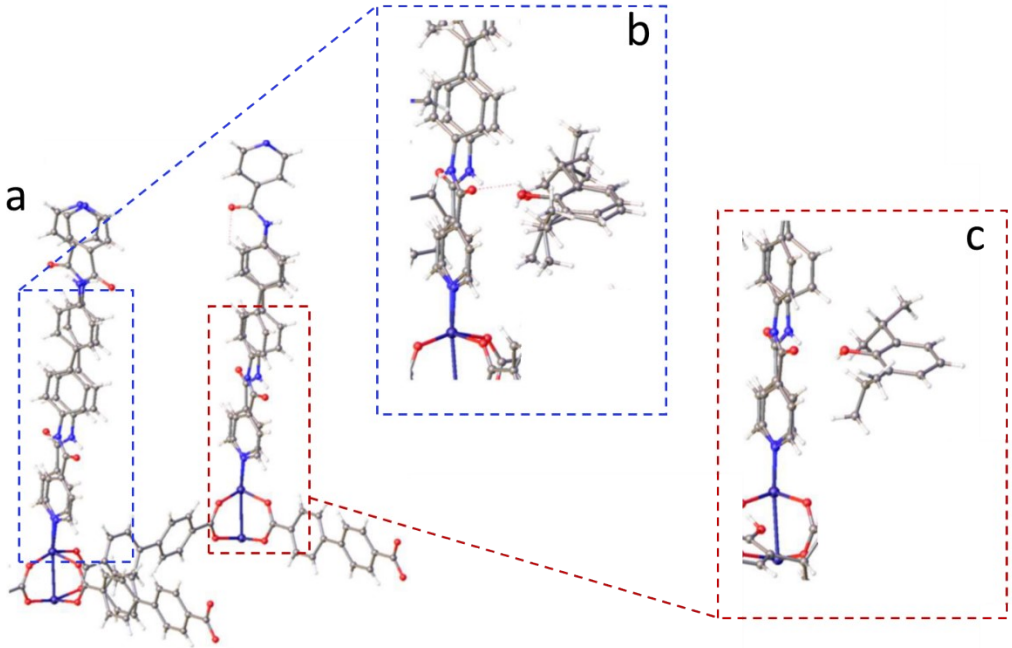

Figure SI3: Disorder of the acentric net in PUM68@propofol a) a-net after propofol inclusion: disorder of amidic ligands; b) and c) propofol interaction with the disordered net.

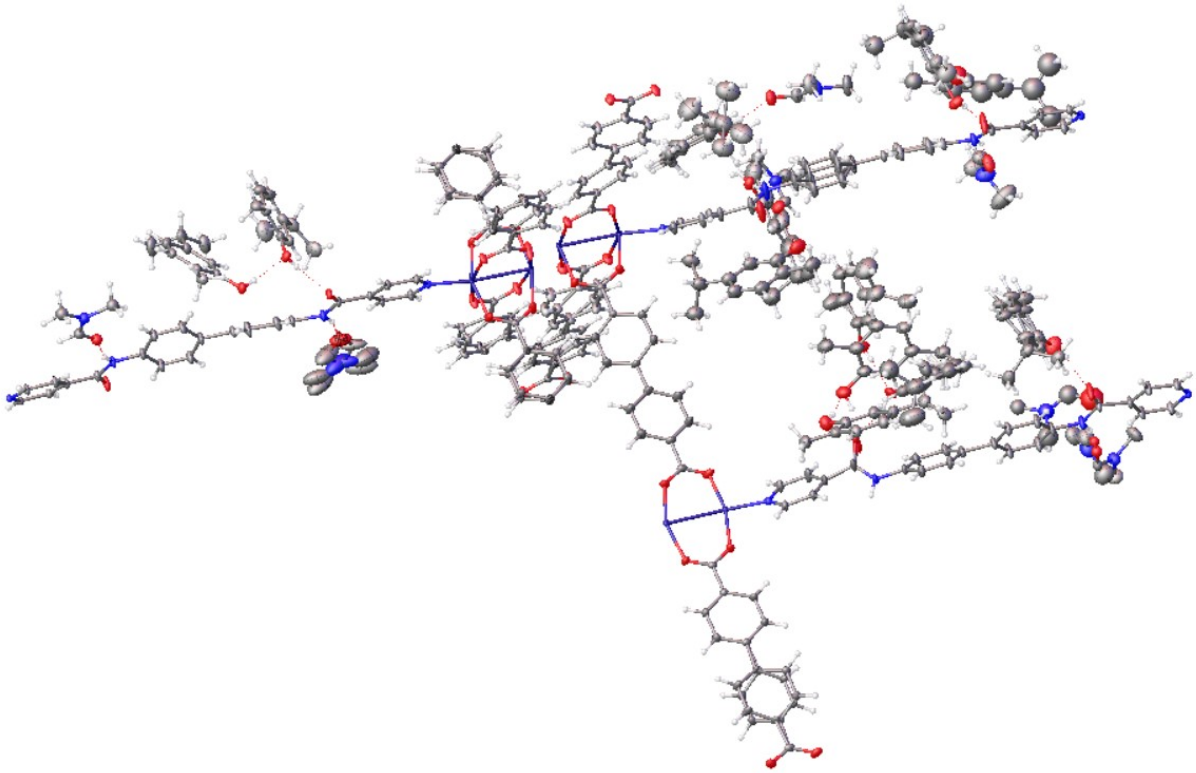

Figure SI4. The asymmetric unit of as synthesized PUM168@carvacrol. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity. Carvacrol guest molecule observed and resilient DMF molecules are also displayed. Colour code: C=grey, O=red, N=blue, H=white, Zn=purple. Disorder of the guest molecules and the a-nets are fully reported.

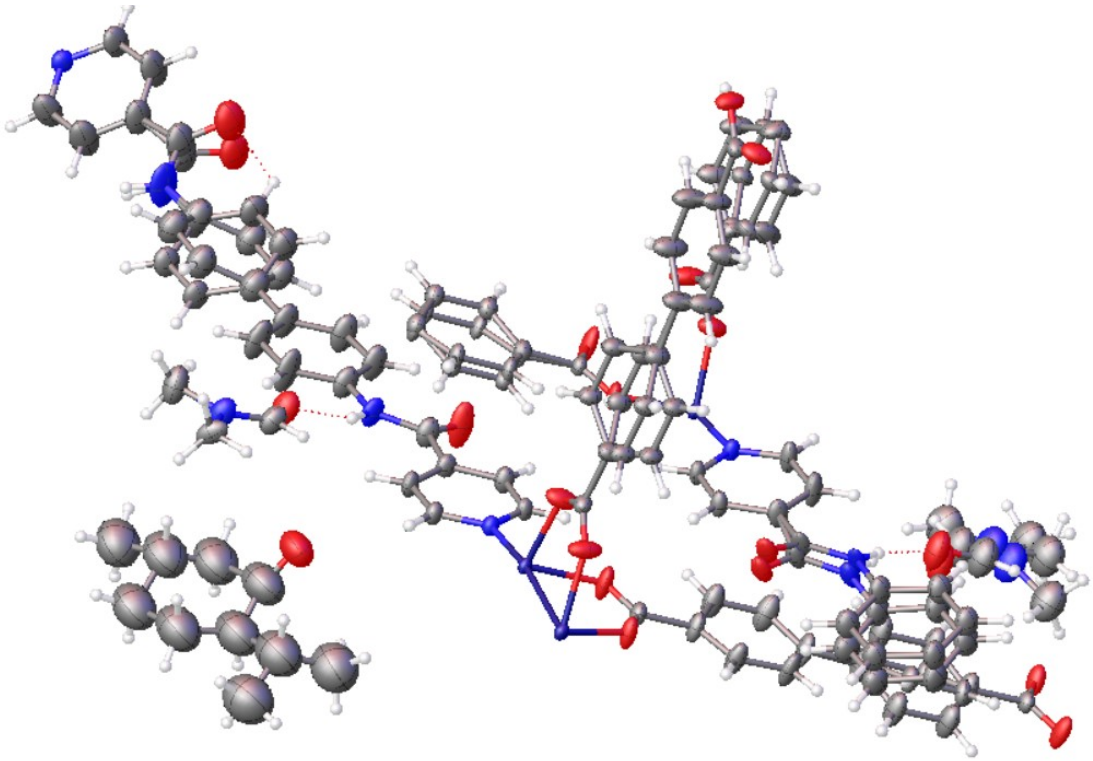

Figure SI5. The asymmetric unit of as synthesized PUM168@menthone. All non-hydrogen atoms shown as ellipsoids at the 50% probability level. H atoms (isotropically refined) are reported in ball-and-stick style for the sake of clarity. Menthone guest molecule observed and resilient DMF molecules are also displayed. Colour code: C=grey, O=red, N=blue, H=white, Zn=purple.

2.2 Specific details of structure refinement

For the structural refinement of **PUM168**@propofol, **PUM168**@carvacrol and **PUM168**@menthone the bond geometry of disordered propofol, carvacrol and menthone molecules, respectively, have been idealized by applying appropriate constraints and restraints. In case of **PUM168**@menthone, 665 e^-/cell residual unexplained electron density has been modelled by using the OLEX2[1] mask procedure.

2.3 Check cif

Table SI2: PUM168@propofol checkcif

Bond precision: C-C = 0.0047 A Wavelength=0.70000

Cell: a=15.263(3) b=30.497(6) c=26.950(5)
alpha=89.20(3) beta=82.16(3) gamma=87.80(3)
Temperature: 100 K

	Calculated	Reported
Volume	12418(4)	12417(4)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C104.50 H68.50 N8 O20 Zn4, C52 H34 N4 O10 Zn2, 6.75(C3 H4.50 O0	0.75(C104.5 H68.5 N8 O20 Zn4), 3.25(C12 H18 O), 0.5(C9 H9.25 O0
Sum formula	C253.25 H251.50 N15.25 O40.50 Zn6	C126.62 H125.75 N7.62 O20.25 Zn3
Mr	4549.03	2274.45
Dx,g cm-3	1.217	1.217
Z	2	4
Mu (mm-1)	0.615	0.618
F000	4763.5	4764.0
F000'	4768.85	
h,k,lmax	18,37,32	18,37,32
Nref	47176	46776
Tmin,Tmax		
Tmin'		

Correction method= Not given

Data completeness= 0.992 Theta(max)= 25.266

R(reflections)= 0.0898(44338) wR2(reflections)= 0.2716(46776)

S = 1.042 Npar= 3272

Table SI3: PUM168@carvacrol checkcif

Bond precision: C-C = 0.0024 A Wavelength=0.70000

Cell: a=21.473(5) b=21.5530(9) c=26.886(2)
alpha=94.896(3) beta=102.406(8) gamma=89.986(14)
Temperature: 100 K

	Calculated	Reported
Volume	12106(3)	12106(3)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	, C52 H34 N4 O10 Zn2, 8.8(C2 H2.80 O0.20), C4.50 ? H6.10 O0.45, C	
Sum formula	C260.70 H264.60 N17.90 O44.60 Zn6	C130.35 H132.30 N8.95 O22.30 Zn3
Mr	4754.45	2377.15
Dx,g cm-3	1.304	1.304
Z	2	4
Mu (mm-1)	0.636	0.638
F000	4981.8	4982.0
F000'	4987.26	
h,k,lmax	28,28,35	28,28,35
Nref	60134	59226
Tmin,Tmax	0.941,0.969	
Tmin'	0.938	

Correction method= Not given

Data completeness= 0.985 Theta(max)= 27.818

R(reflections)= 0.0534(53253) wR2(reflections)= 0.1462(59226)

S = 1.038 Npar= 3874

Table SI4: PUM168@menthone checkcif

Bond precision: C-C = 0.0085 A Wavelength=0.70000

Cell: a=15.186(3) b=15.210(3) c=26.964(5)
alpha=91.53(3) beta=102.04(3) gamma=91.69(3)
Temperature: 100 K

	Calculated	Reported
Volume	6085(2)	6085(2)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C52 H34 N4 O10 Zn2, C26 H17 N2 O5 Zn, C10 H18 O, 2(C1.50 H3.50	3(C26 H17 N2 O5 Zn), 2(C3 H7 N O), C10 H18 O
Sum formula	C94 H83 N8 O18 Zn3 [+ solvent]	C94 H83 N8 O18 Zn3
Mr	1808.86	1808.79
Dx,g cm-3	0.987	0.987
Z	2	2
Mu (mm-1)	0.613	0.615
F000	1874.0	1874.0
F000'	1876.50	
h,k,lmax	18,18,32	18,18,32
Nref	23112	22884
Tmin,Tmax		
Tmin'		

Correction method= Not given

Data completeness= 0.990 Theta(max)= 25.265

R(reflections)= 0.0705(22291) wR2(reflections)= 0.2007(22884)

S = 1.044 Npar= 1419

2.4 Host-Guest and Guest-Guest interactions

Table SI2: Host-Guest interactions

	Guest	*Host*	*Contact (Å)*
PUM168@propofol	Propofol-B	a-net	2.857 (3)
	Propofol-C	a-net	3.045 (4)
	Propofol-D	a-net	3.230 (3)
	Propofol-F	a-net	2.927 (8)
	Propofol-G	a-net	2.215 (5)
	Propofol-H	a-net	3.006 (6)
	DMF-I	c-net	2.921 (2)
	DMF-II	c-net	2.865 (7)
PUM168@carvacrol	Carvacrol-A	c-net	2.783 (4)
	Carvacrol-B	a-net	3.063 (2)
	Carvacrol-C	a-net	2.737 (3)
	Carvacrol-E	a-net	2.808 (4)
	Carvacrol-F	a-net	3.013 (3)
	Carvacrol-H	a-net	2.694 (2)
	Carvacrol-I	a-net	3.469 (2)
	DMF-I	c-net	2.930 (1)
	DMF-II	c-net	2.853 (2)
	DMF-II	a-net	3.027 (3)
	DMF-V	a-net	2.916 (8)
PUM168@menthone	DMF-I	c-net	2.863 (2)
	DMF-II	a-net	2.991 (2)

Table SI2: Guest-Guest interactions

	Guest	*Guest*	*Contact (Å)*
PUM168@propofol	Propofol-A	Propofol-A’	2.940 (2)
	Propofol-E	Propofol-E’	2.912 (4)
	Propofol-H	Propofol-I	2.669 (4)
	DMF-II	Propofol-I	2.624 (2)
PUM168@carvacrol	Carvacrol-A	Carvacrol-B	2.878 (2)
	Carvacrol-C	Carvacrol-D	2.825 (7)
	Carvacrol-F	Carvacrol-G	2.760 (2)
	DMF-IV	Carvacrol-G	2.695 (4)
	DMF-VI	Carvacrol-I	2.728 (6)

2.5 Guests occupancy

	Guest	Occupancy
PUM168@propofol	Propofol-A	1
	Propofol-B	1
	Propofol-C_1	0.75
	Propofol-C_2	0.25
	Propofol-D	0.25
	Propofol-E	0.25
	Propofol-G	0.75
	Propofol-F	1
	Propofol-H	1
	Propofol-I	1
	Propofol-L	1
PUM168@carvacrol	Carvacrol-A	1
	Carvacrol-B	1
	Carvacrol-C_1	0.7
	Carvacrol-C_2	0.3
	Carvacrol-D_1	0.7
	Carvacrol-D_2	0.3
	Carvacrol-E_1	0.6
	Carvacrol-E_2	0.4
	Carvacrol-F_1	0.8
	Carvacrol-F_2	0.2
	Carvacrol-G_1	0.5
	Carvacrol-G_2	0.5
	Carvacrol-H	1
	Carvacrol-I_1	0.45
	Carvacrol-I_2	0.25
PUM168@menthone	Menthone-A	1

2.6 Porosity and guest loading details

The analysis of the shape of the pores in PUM168 have been reported in our previous work. As showed in the figure below (extracted from the Supporting Information of D. Balestri, P. P. Mazzeo, C. Carraro, N. Demitri, P. Pelagatti and A. Bacchi, Angew. Chem. Int. Ed., 2019, 58, 17342–17350), the pores are characterized by a size of 7.06 Å and 15.09 Å.

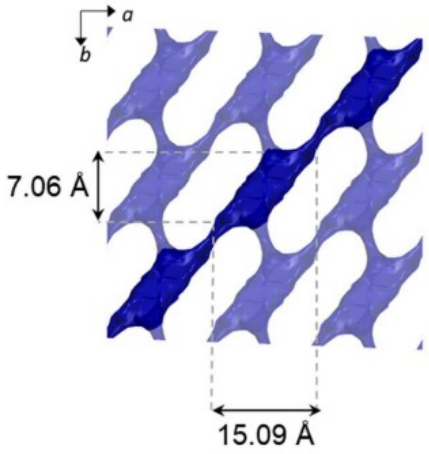

Figure SI6. PUM168 pores shape analysis. Representation of the pores in PUM168 along the crystallographic c-axis.

Considering the calculation of the potential voids of the loaded material (i.e the volume of the pored once they have been cleaned from framework disorder and solvent/guest molecules) and we divide it by the molecular volume of the guest of interest we obtain and efficiency parameters for the loading process.

Volume of Pores [2]		Molecular volume of Guest [3]		Maxim number of guests per ASU [a]	Efficiency parameter [b]
PUM168@Propofol	6782.49 Å³	**Propofol**	167.5 Å³	12	30%
PUM168@Carvacrol	6279.62 Å³	**Carvacrol**	161.2 Å³	11	32%

[a] the maximum number of guest has been calculated considering a packing factor of 0.6
b Efficiency parameter calculated as the ration between the number of guests experimentally observed over the Maximum number of guests per ASU. This also takes into account the presence of resilient pristine solvent molecules.

In the case of menthone, the high unmodelled residual electron density does not allow for the same calculation.

1 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.

2 C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. Mccabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Cryst*, 2020, **53**, 226–235

3 B. Jayaram, Tanya Singh, Goutam Mukherjee, Abhinav Mathur, Shashank Shekhar, and Vandana Shekhar, *BMC Bioinformatics*, **2012**, *13*, S7.