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Exploring binding preferences in co-crystals of conformationally flexible multitopic ligands

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Supplementary Information

Table of content

Table 1. Crystallographic data for the cocrystals.

Code	**3,4:Mal**	**2.3:Adp**	**3,4:Suc.H_2O**	**2,3:Azl**	**2,3:Mal**
Formula moiety	$(C_{12}H_{10}N_4O)$ $(C_3H_4O_4)$	$(C_{12}H_{10}N_4O)_2$ $(C_6H_{10}O_4)$	$(C_{12}H_{10}N_4O)$ $(C_4H_6O_4)$ (H_2O)	$(C_{12}H_{10}N_4O)$ $(C_9H_{16}O_4)$	$(C_{12}H_{10}N_4O)$ $(C_3H_4O_4)$
Empirical formula	$C_{15}H_{14}N_4O_5$	$C_{30}H_{30}N_8O_6$	$C_{16}H_{18}N_4O_6$	$C_{21}H_{26}N_4O_5$	$C_{15}H_{14}N_4O_5$
Molecular weight	330.30	598.62	362.34	414.46	330.30
Color, Habit	Colorless, Plate	Colorless, Prism	Colorless, Plate	Colorless, Prism	Colorless, Prism
Crystal system	Triclinic	Triclinic	Orthorhombic	Triclinic	Triclinic
Space group, *Z*	*P*$\bar{1}$, 2	*P*$\bar{1}$, 1	*Pbca*, 8	*P*$\bar{1}$, 2	*P*$\bar{1}$, 2
a, Å	7.0290(10)	5.9660(5)	7.1160(8)	8.5041(12)	8.0953(12)
b, Å	10.5537(15)	7.2613(6)	13.0840(16)	9.6723(14)	9.9439(14)
c, Å	10.8826(15)	16.8960(14)	36.062(5)	14.013(2)	10.1459(15)
α, º	73.431(5)	89.858(2)	90	80.742(6)	99.924(6)
β, º	76.424(5)	80.013(3)	90	81.368(6)	106.674(6)
γ, º	71.357(5)	79.638(2)	90	68.770(5)	100.865(6)
Volume, $Å^3$	723.95(18)	708.79(10)	3357.6(7)	1055.1(3)	745.78(19)
Density, g/cm^3	1.515	1.402	1.434	1.305	1.471
T, ºK	120(2)	120(2)	120(2)	120(2)	120(2)
Crystal size, min x mid x max	0.08 x 0.26 x 0.34	0.30 x 0.36 x 0.42	0.08 x 0.28 x 0.32	0.16 x 0.26 x 0.34	0.18 x 0.26 x 0.32
X-ray wavelength, Å	0.71073	0.71073	1.54178	1.54178	1.54178
μ, mm^{-1}	0.117	0.101	0.945	0.780	0.957
Trans min / max	0.9614 / 0.9907	0.9588 / 0.9703	0.7519 / 0.9282	0.7773 / 0.8853	0.7493 / 0.8466
θ_{min}, º	1.98	2.45	2.45	4.94	4.67
θ_{max}, º	32.66	32.11	70.19	69.60	68.55
Reflections					
collected	16031	15145	29624	16331	11844
independent	4726	4623	3060	3704	2638

observed	3644	4145	2439	3399	2360
R_{int}	0.0281	0.0213	0.0861	0.0360	0.0392
Threshold expression	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$
No. parameters	254	205	250	281	226
No. restraints	0	0	0	0	0
R_1 (observed)	0.0448	0.0435	0.0552	0.0378	0.0379
wR_2 (all)	0.1305	0.1198	0.1560	0.1052	0.1137
Goodness of fit (all)	1.066	0.953	1.125	1.109	1.040
ρ_{max}, ρ_{min}, e Å^{-3}	0.504, -0.375	0.367, -0.366	0.249, -0.299	0.227, -0.179	0.200, -0.334
2θ limit, º	30.00	30.00	70.00	67.50	67.50
Completeness to 2θ limit	0.992	0.982	0.963	0.96	0.974

Code	**3,3:Dod.H_2O**	**3,4:Glu.2 H_2O**	**4,2:Sub.2 H_2O**	**3,3:Seb.H_2O**	**4,2:Adp.2 H_2O**
Formula moiety	$(C_{12}H_{10}N_4O)$ $(C_{12}H_{22}O_4)$ (H_2O)	$(C_{12}H_{10}N_4O)$ $(C_5H_8O_4)$ $(H_2O)_2$	$(C_{12}H_{10}N_4O)_2$ $(C_8H_{14}O_4)$ $(H_2O)_2$	$(C_{12}H_{10}N_4O)$ $(C_{10}H_{18}O_4)$ (H_2O)	$(C_{12}H_{10}N_4O)_2$ $(C_6H_{10}O_4)$ $(H_2O)_2$
Empirical formula	$C_{24}H_{34}N_4O_6$	$C_{17}H_{22}N_4O_7$	$C_{32}H_{38}N_8O_8$	$C_{22}H_{30}N_4O_6$	$C_{30}H_{34}N_8O_8$
Molecular weight	474.55	394.39	662.70	446.50	634.65
Color, Habit	Colorless, Plate	Colorless, Prism	Colorless, Prism	Colorless, Plate	Colorless, Plate
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic	Triclinic
Space group, *Z*	*P*$\bar{1}$, 2	*P*$\bar{1}$, 4	*P*$\bar{1}$, 1	*P*$\bar{1}$, 4	*P*$\bar{1}$, 1
a, Å	6.9300(8)	10.9929(10)	6.6774(11)	6.9504(10)	6.5986(6)
b, Å	7.8773(10)	11.4742(10)	8.2196(14)	14.170(2)	8.0173(8)
c, Å	24.680(3)	16.1087(14)	15.972(3)	23.788(3)	15.3396(14)
α, º	85.562(6)	102.095(3)	81.888(7)	79.555(9)	97.862(4)
β, º	83.394(6)	108.567(4)	83.771(8)	84.610(8)	101.861(3)
γ, º	66.198(5)	95.615(3)	74.805(7)	89.821(9)	104.541(3)
Volume, Å^3	1223.8(3)	1853.4(3)	835.2(2)	2293.7(6)	753.39(12)
Density, g/cm^3	1.288	1.413	1.318	1.293	1.399
T, ºK	120(2)	120(2)	120(2)	180(2)	120(2)
Crystal size, min x mid x max	0.12 x 0.28 x 0.32	0.14 x 0.26 x 0.38	0.16 x 0.22 x 0.32	0.12 x 0.20 x 0.28	0.10 x 0.24 x 0.44
X-ray wavelength, Å	1.54178	0.71073	1.54178	1.54178	0.71073
μ, mm^{-1}	0.767	0.111	0.804	0.787	0.104
Trans min / max	0.7913 / 0.9135	0.9590 / 0.9846	0.7829 / 0.8821	0.8097 / 0.9115	0.9557 / 0.9897
θ_{min}, º	1.80	1.38	2.80	1.90	1.38
θ_{max}, º	67.72	32.60	68.58	68.58	33.17
Reflections					
collected	16550	37645	13228	36604	18394
independent	4136	11890	2996	8223	5103

observed	3787	7481	2754	5569	4166
R_{int}	0.0359	0.0491	0.0354	0.0802	0.0224
Threshold expression	> 2$\sigma(I)$	> 2$\sigma(I)$	> 2$\sigma(I)$	> 2$\sigma(I)$	> 2$\sigma(I)$
No. parameters	322	548	229	605	220
No. restraints	0	0	0	0	0
R_1 (observed)	0.0452	0.0580	0.0390	0.0764	0.0426
wR_2 (all)	0.1187	0.1839	0.1069	0.2466	0.1329
Goodness of fit (all)	1.064	1.054	1.047	1.447	1.058
ρ_{max}, ρ_{min}, e Å^{-3}	0.416, -0.265	0.528, -0.389	0.447, -0.286	0.199, -0.316	0.414, -0.260
2θ limit, º	67.50	30.00	67.50	67.50	30.00
Completeness to 2θ limit	0.934	0.98	0.986	0.985	0.999

Code	**2,3:Glu**	**4,2:Azl.2 H_2O**	**2,3:Pim**
Formula moiety	$(C_{12}H_{10}N_4O)$ $(C_5H_8O_4)$	$(C_{12}H_{10}N_4O)_2$ $(C_9H_{16}O_4)$ $(H_2O)_2$	$(C_{12}H_{10}N_4O)$ $(C_7H_{12}O_4)$
Empirical formula	$C_{17}H_{18}N_4O_5$	$C_{33}H_{40}N_8O_8$	$C_{19}H_{22}N_4O_5$
Molecular weight	358.35	676.73	386.41
Color, Habit	Colorless, Plate	Colorless, Plate	Colorless, Plate
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group, *Z*	*P*2(1)/*c*, 4	*P*2(1)/*c*, 4	*P*2(1)/*c*, 4
a, Å	20.694(3)	36.802(8)	5.5981(7)
b, Å	5.5714(8)	7.2815(14)	45.389(5)
c, Å	14.954(2)	12.533(3)	7.3036(8)
α, º	90	90	90

β, º	105.047(7)	92.978(8)	98.469(5)
γ, º	90	90	90
Volume, Å^3	1665.0(4)	3354.1(13)	1835.5(4)
Density, g/cm^3	1.430	1.340	1.398
T, ºK	120(2)	120(2)	120(2)
Crystal size, min x mid x max	0.10 x 0.22 x 0.40	0.10 x 0.36 x 0.40	0.06 x 0.28 x 0.36
X-ray wavelength, Å	0.71073	0.71073	0.71073
μ, mm^{-1}	0.108	0.098	0.103
Trans min / max	0.9582 / 0.9893	0.9619 / 0.9903	0.9638 / 0.9938
θ_{min}, º	1.02	1.11	2.86
θ_{max}, º	31.51	31.56	32.11
Reflections			
collected	24390	68658	31436
independent	5305	10990	5805
observed	3401	8106	4314
R_{int}	0.0850	0.0552	0.0406
Threshold expression	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$
No. parameters	244	494	259
No. restraints	0	37	0
R_1 (observed)	0.0703	0.0995	0.0557
wR_2 (all)	0.2140	0.3093	0.1558
Goodness of fit (all)	1.216	2.015	1.048
ρ_{max}, ρ_{min}, e Å^{-3}	0.531, -0.550	0.737, -0.486	0.566, -0.269
2θ limit, º	30.00	31.56	29.00
Completeness to 2θ limit	0.99	0.978	0.943

Crystallography Experimental Details

Datasets were collected on a Bruker Kappa APEX II system using CuKα radiation (**3,4:Suc.H_2O**; **2,3:Azl**; **2,3:Mal**; **3,3:Dod.H_2O**; **4,2:Sub.2 H_2O**; **3,3:Seb.H_2O**), or on a Bruker APEX II system using MoKα radiation (**3,4:Mal**; **2,3:Adp**; **3,4:Glu.2 H_2O**; **4,2:Adp.2 H_2O**; **2,3:Glu**; **4,2:Azl.2 H_2O**; **2,3:Pim**). Data were collected using APEX2 software.[i] Initial cell constants were found by small widely separated "matrix" runs. Data collection strategies were determined using COSMO.[ii] Scan speed and scan widths were chosen based on scattering power and peak rocking curves. All datasets except **3,3:Seb.H_2O** (-93 °C) were collected at -153 °C using an Oxford Cryostream low-temperature device.

Unit cell constants and orientation matrix were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT,[iii] using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. Multi-scan absorption corrections were performed with SADABS.[iv]

Data were reduced with SHELXTL.[v] The structures were solved in all cases by direct methods without incident. Except as noted, hydrogen atoms were located in idealized positions and were treated with a riding model. All non-hydrogen atoms were assigned anisotropic thermal parameters. Refinements continued to convergence, using the recommended weighting schemes.

3,4:Mal: Part of the dicarboxylic acid molecule is disordered over two closely related positions, representing wobble around the C-C bond. Thermal parameters were pairwise constrained using the EADP command. Coordinates of the amide hydrogen atom H17 and the carboxylic acid hydrogen atom H31 were allowed to refine.

2,3:Adp: Coordinates of the amide hydrogen atom H17 and the carboxylic acid hydrogen atom H31 were allowed to refine.

3,4:Suc.H_2O: Coordinates of the amide hydrogen atom H17, the carboxylic acid hydrogen atoms H31 and H34, and the water molecule hydrogen atoms H1A and H1B were allowed to refine.

2,3:Azl: Coordinates of the amide hydrogen atom H17 and the carboxylic acid hydrogen atoms H31 and H39 were allowed to refine.

2,3:Mal: Coordinates of the amide hydrogen atom H17 and the carboxylic acid hydrogen atoms H31 and H33 were allowed to refine.

3,3:Dod.H_2O: Coordinates of the amide hydrogen atom H17, the carboxylic acid hydrogen atoms H31 and H42, and the water molecule hydrogen atoms H1A and H1B were allowed to refine.

3,4:Glu.2 H_2O: Coordinates of the amide hydrogen atoms H17_1 and H17_2, the carboxylic acid hydrogen atoms H31_1, H31_2, H35_1 and H35_2, and the water molecule hydrogen atoms H1A_1, H1B_1, H2A_1, H2B_1, H3A_2, H3B_2, H4A_2 and H4B_2 were allowed to refine.

4,2:Sub.2 H_2O: Coordinates of the amide hydrogen atom H17, the carboxylic acid hydrogen atom H31, and the water molecule hydrogen atoms H1A and H1B were allowed to refine.

3,3:Seb.H_2O: The asymmetric unit contains two molecules each of the pyridine-based ligand, aliphatic dicarboxylic acid and water. One of the pyridine-based ligand molecules is disordered. The same coordinates have been utilized for atoms occupying the same site using the EXYZ command. Thermal parameters for closely located atoms were pairwise constrained using the EADP command. Coordinates of the amide hydrogen atoms H17_1 and H17_2, the carboxylic acid hydrogen atoms H31_1, H40_1, H31_2 and H40_2, and the water molecule hydrogen atoms H1A_1, H1B_1, H1A_2 and H1B_2 were allowed to refine.

4,2:Adp.2 H_2O: Coordinates of the amide hydrogen atom H17, the carboxylic acid hydrogen atom H31, and the water molecule hydrogen atoms H1A and H1B were allowed to refine.

2,3:Glu: Coordinates of the amide hydrogen atom H17 and the carboxylic acid hydrogen atoms H31 and H35 were allowed to refine.

4,2:Azl.2 H_2O: The asymmetric unit contains two molecules each of the pyridine-based ligand and water along with one molecule of the aliphatic dicarboxylic acid. The entire aliphatic dicarboxylic acid molecule is disordered over two closely related positions, thus representing different orientations. Relative populations were allowed to refine. Thermal parameters were pairwise constrained using EADP commands. Geometry of the aliphatic carbon chain was restrained using the SAME command. The bond distances were fixed to idealized distances using the DFIX command. Coordinates of the amide hydrogen atoms H17 and H37, the carboxylic acid

hydrogen atom H51, and the water molecule hydrogen atoms H1A, H1B, H2A and H2B were allowed to refine.

2,3:Pim: Coordinates of the amide hydrogen atom H17 and the carboxylic acid hydrogen atoms H31 and H37 were allowed to refine.

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[i] APEX2 v2013.10-0, © 2013, Bruker Analytical X-ray Systems, Madison, WI.

[ii] COSMO v1.61, © 1999 - 2009, Bruker Analytical X-ray Systems, Madison, WI.

[iii] SAINT v8.34a, © 1997 - 2013, Bruker Analytical X-ray Systems, Madison, WI.

[iv] SADABS v2012/1, © 2012, Bruker Analytical X-ray Systems, Madison, WI.

[v] SHELXTL v2008/4, © 2008, Bruker Analytical X-ray Systems, Madison, WI.