

Supplementary Information

Synthon trends according to acid strength and geometry in salts of *N*-heterocyclic bases

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Experimental

Preparation of salts derived from N-heterocyclic bases

Chloride (**A1**) and bromide (**A2**) salts of aminopyrazine (ampyz) and the bis(dihydrogen phosphate) salt of 1,2-bis(4-pyridyl)ethane (BPE) (**B2**) were prepared as follows. Certain quantity of ampyz (5.1 and 5.5 mg) and BPE (2.6 mg) was dissolved in 5 mL of a water/isopropyl alcohol (1:1 v/v) mixture acidified with the respective acid source [82.8 μL of HCl (37% m/m), 113 μL of HBr (48% m/m) and 67.4 μL of H_3PO_4 (85 % m/m)]. After slow evaporation of the described solutions (25 days, 20 °C), transparent plate crystals were obtained at the bottom of the glass crystallizer.

The salts of ampyz with isopropyl sulfuric (**A3**), trifluoroacetic (TFA) (**A4**), trichloroacetic (TCA) (**A5**), and phosphoric (**A6**) acids, the BPE salt with hydrobromic acid (**B1**), and the phosphoric acid cocrystal of the BPE dihydrogen phosphate salt (**B3**) were obtained dissolving the *N*-heterocyclic compound (12.1, 10.2, 11.1 and 10.3 mg of ampyz and 2.3 and 2.2 mg of BPE, respectively) in 10 mL of isopropyl alcohol acidified with respective acid source [56.1 μL of H_2SO_4 (95-98% m/m), 76.8 μL of TFA, 1.3 mg of TCA, 67.4 μL of H_3PO_4 (85 % m/m), and 113 μL of HBr (48% m/m)]. Again, after slow evaporation of the described solutions (15 days, 20 °C), transparent plate crystals were obtained at the bottom of the glass crystallizer.

Structure determination of salts and cocrystal of salt derived from N-heterocyclic compounds

The plate shape crystals were isolated from glass crystallizer and mounted on a μm loop (MiTeGen MicroLoops™). Next, each crystal was centered on the goniostat of a Bruker-AXS Kappa Duo diffractometer with an APEX II CCD detector. $\text{MoK}\alpha$ (except for **A3** which was used $\text{CuK}\alpha$) radiation from an $\text{I}\mu\text{S}$ microsource with multilayer optics was employed for X-ray intensities collect at 23°C. The diffraction frames were recorded by ϕ and ω scans using APEX2 software¹ for collect strategy and frames acquisition. Raw dataset treatment including indexing, integrating, reducing and scaling of Bragg reflections was also performed using the program APEX2.¹ Multi-scan absorption correction has been employed to all dataset.² The structure was solved by direct methods with SHELXS-2014³, wherein C, N, O, F, Cl, Br, S and P were directly assigned from the electron density Fourier map. The initial model was refined by the full-matrix least squares method using F^2 with SHELXL-2014.³ Anisotropic and isotropic atomic displacement parameters were set for non-hydrogen and hydrogen atoms, respectively. Each hydrogen had its isotropic displacement parameter fixed [$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C or N})$ or $1.5U_{\text{eq}}(\text{C}_{\text{methyl}} \text{ or O})$]. Hydrogens bonded to carbons were positioned stereochemically with constrained C-H bond lengths of 0.93 Å (aromatic), 0.98 Å (methine), and 0.96 Å (methyl). Hydrogens bonded to N and O were also constrained with bond lengths of 0.86 Å (N-H) and 0.82 Å (O-H), but they were first identified in difference Fourier map and checked for hydrogen bonding directionality. Coordinates of all hydrogens oscillate as those of the bonded atom, followed the riding model. In addition, the central double-bonded carbons were found to be disordered over two sets of 50% occupancy sites each in **B1** and **B3**. Likewise, the methine carbon from both isopropyl sulfate counterions present in the asymmetric unit of **A3** was refined over two sites of 60% and 40% occupancy each. The programs MERCURY⁴ and ORTEP-3⁵ were used within the WinGX⁵ software package to prepare artwork representations.

Theoretical calculations of synthons energy

All calculations were performed using Gaussian 09.⁶ The synthons were extracted out from our crystal structures, except for the secondary ones, in which their input were created using CHIMERA⁷. The energy of synthons was obtained for aggregates prior and after full geometry optimization. These calculations were all carried out at M06-2X/6-31+G** level of theory. The comparison of synthons energy was made through subtraction of the resulted energy of full optimization geometry of synthons, except for $\Delta E_{\text{I} \rightarrow \text{I}'}$ which geometry optimization of I' did not converge.

Table S1. Crystal data and refinement statistics of salts derived from *N*-heterocyclic bases.

		A1	A2	A3	A4	A5	A6	B1	B2	B3
Chemical formula		C ₄ H ₆ N ₃ Cl	C ₄ H ₆ N ₃ Br	C ₇ H ₁₃ N ₃ O ₄ S	C ₆ H ₆ F ₃ N ₃ O ₂	C ₆ H ₆ Cl ₃ N ₃ O ₂	C ₄ H ₈ N ₃ PO ₄	C ₁₂ H ₁₂ Br ₂ N ₂	C ₁₂ H ₁₆ N ₂ O ₈ P ₂	C ₁₂ H ₁₉ N ₂ O ₁₂ P ₃
Fw (g.mol ⁻¹)		131.57	176.02	235.26	209.14	258.49	193.1	344.04	378.21	476.20
Cryst syst		Triclinic	Triclinic	Monoclinic	Triclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
Space group		<i>P</i> -1	<i>P</i> -1	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> 2/ <i>c</i>
Z		2	2	8	4	4	4	2	2	4
Unit cell dimension	<i>a</i> (Å)	4.9992(4)	5.0554(9)	9.0017(7)	8.778(8)	13.6957(3)	4.5002(2)	5.1052(8)	9.2640(7)	21.4140(16)
	<i>b</i> (Å)	7.3893(7)	7.5644(13)	21.128(2)	10.165(9)	5.53110(10)	8.7726(3)	10.2491(15)	4.7949(3)	9.4256(9)
	<i>c</i> (Å)	8.8313(8)	9.0290(14)	11.7627(9)	10.918(9)	14.3450(3)	19.7107(8)	12.6953(18)	17.7033(13)	9.4548(7)
	α (°)	72.451(6)	72.096(11)	90	78.86(2)	90	90	90	90	90
	β (°)	78.656(5)	79.191(11)	90.617(5)	69.57(3)	109.2240(10)	90	93.053(2)	90.536(2)	99.380(5)
	γ (°)	79.410(6)	80.625(11)	90	72.29(4)	90	90	90	90	90
<i>V</i> (Å ³)		302.26(5)	320.68(10)	2237.0(3)	865.5(13)	1026.07(4)	778.15(5)	663.32(17)	786.35(10)	1882.8(3)
ρ_{calc} (g.cm ⁻³)		1.446	1.813	1.397	1.605	1.673	1.648	1.722	1.597	1.680
Abs. coefficient μ (mm ⁻¹)		0.520	6.304	2.626	0.162	0.870	0.334	6.086	0.322	0.384
θ range for data collection (°)		2.447 - 29.178	2.396 - 25.428	4.185 - 66.615	2.000 - 25.039	1.784 - 25.351	2.066 - 25.352	2.555 - 25.332	2.301 - 25.339	1.928 - 25.049
index ranges	<i>h</i>	-6 to 6	-5 to 6	-10 to 10	-9 to 10	-16 to 16	-4 to 5	-6 to 6	-11 to 11	-24 to 24
	<i>k</i>	-9 to 10	-8 to 9	-24 to 25	-7 to 12	-6 to 6	-10 to 5	-10 to 12	-5 to 5	-11 to 6
	<i>l</i>	-12 to 11	-10 to 10	-13 to 12	-11 to 12	-17 to 17	-17 to 23	-12 to 15	-21 to 20	-11 to 10
Data collected		4926	3007	10410	5968	10544	4005	2912	3423	3051
Unique reflections		1565	1163	3851	2963	1864	1420	1203	1408	1626
Symmetry factor (R_{int})		0.0324	0.0346	0.0344	0.0599	0.0197	0.022	0.0441	0.0344	0.0255
Completeness to θ_{max} (%)		99.3	99.5	97.5	96.9	98.9	99.4	99.3	98.2	97.4
<i>F</i> (000)		136	172	992	424	520	400	336	392	984
Refined parameters		74	73	289	298	127	109	82	109	141
Goodness-of-fit on F^2 (<i>S</i>)		1.179	1.088	1.274	1.027	1.049	1.065	1.057	1.076	1.037
Final R_I factor [$I > 2\sigma(I)$]		0.0631	0.0259	0.0923	0.0804	0.0369	0.0279	0.0367	0.0477	0.0435
wR_2 factor (all data)		0.2115	0.0642	0.3268	0.2692	0.1012	0.0687	0.1050	0.1193	0.1143
Largest diff. peak / hole ($e \text{ \AA}^{-3}$)		0.591/ -0.286	0.602/ -0.369	0.935/ -0.584	0.280/ -0.252	0.470/ -0.390	0.160/ -0.233	0.492/ -0.542	0.728/ -0.325	0.327/ -0.329
CCDC deposit no.		1566067	1566063	1566066	1566062	1566064	1566061	1566068	1566060	1566065

Table S2. Metrics of the main intermolecular contacts found in crystal forms of ampyz salts.

D-H...A	D-H'/ Å	H...A/ Å	D...A/ Å	D- H...A/°
A1 or A2				
N ₂ -H _a ...N ₁	0.86	2.22	3.081(3)	168
		2.23	3.469(3)	169
N ₂ -H _b ...X ₁	0.86	2.49	3.303(4)	157
		2.66	3.469(3)	
N ₄ -H ₄ ...X ₁	0.86	2.17	3.001(3)	162
		2.35	3.171(3)	160
C ₃ -H ₃ ...X ₁	0.93	2.84	3.606(5)	140
		2.96	3.738(4)	142
C ₅ -H ₅ ...X ₁	0.93	2.68	3.574(6)	161
		2.84	3.729(4)	160
A3				
N _{1a} -H _{1a} ...O ₁	0.86	1.82	2.675(6)	169
N _{2a} -H _{a2a} ...O ₆	0.86	2.17	3.004(5)	163
N _{2a} -H _{a2b} ...O ₄	0.86	2.16	2.982(6)	161
N _{1b} -H _{1b} ...O ₅	0.86	1.87	2.706(5)	163
N _{2b} -H _{b2a} ...O ₄	0.86	2.15	2.983(5)	162
N _{2b} -H _{b2b} ...O ₆	0.86	2.12	2.970(6)	171
A4				
N _{2a} -H _{a1} ...O ₂	0.86	1.92	2.759(11)	164
N _{2a} -H _{2a} ...O ₄	0.86	2.00	2.776(10)	149
N _{2'a} -H _{a'1} ...N ₆	0.86	2.25	3.067(11)	158
N _{2'a} -H _{a'2} ...O ₄	0.86	2.29	3.144(10)	172
N _{1a4} -H _{1a} ...O ₁	0.86	1.84	2.697(6)	179
N _{2b} -H _{b1} ...O ₄	0.86	1.98	2.824(9)	167
N _{2b} -H _{b2} ...O ₂	0.86	1.96	2.718(9)	146
N _{2'b} -H _{b'1} ...N _{4a1}	0.86	2.20	3.037(11)	165
N _{2'b} -H _{b'2} ...O ₂	0.86	2.28	3.120(10)	163
N _{1b4} -H _{b1} ...O ₃	0.86	1.83	2.684(6)	172
C _{6a5} -H _{6a5} ...O ₃	0.93	2.46	3.351(7)	160
C _{6b5} -H _{6b5} ...O ₁	0.93	2.46	3.389(7)	174
A5				
N ₁ -H ₁ ...O ₁	0.86	1.87	2.720(2)	172
N ₂ -H _a ...O ₂	0.86	1.98	2.835(3)	174
N ₂ -H _b ...O ₂	0.86	2.06	2.837(4)	150
C ₅ -H ₅ ...Cl ₂	0.93	2.96	3.715(3)	139
C ₆ -H ₆ ...O ₁	0.93	2.64	3.310(4)	130
A6				
N ₁ -H ₁ ...O ₁	0.86	1.83	2.666(3)	165
N ₂ -H _a ...O ₂	0.86	2.09	2.945(3)	171
N ₂ -H _b ...O ₃	0.86	1.98	2.842(3)	174
O ₂ -H _{2p} ...O ₁	0.82	1.73	2.506(3)	157
O ₄ -H _{4p} ...O ₃	0.82	1.73	2.504(3)	157

Table S3. Metrics for the main intermolecular contacts found in the crystal forms of BPE.

D-H...A	D-H/ Å	H...A/ Å	D...A/ Å	D-H...A/°
B1				
N ₁ -H _{1n} ...Br ₁	0.86	2.38	3.179(3)	159
C ₁ -H ₁ ...Br ₁	0.86	2.74	3.562(5)	147
C ₃ -H ₆ ...Br ₁	0.86	2.92	3.700(9)	142
B2				
N ₁ -H _{1n} ...O ₁	0.86	1.70	2.555(3)	178
C ₁ -H ₁ ...O ₁	0.93	2.33	3.229(5)	162
C ₄ -H ₄ ...O ₃	0.93	2.45	3.351(4)	162
O ₂ -H _{2p} ...O ₃	0.82	1.91	2.588(3)	140
O ₄ -H _{4p} ...O ₃	0.82	1.80	2.599(3)	164
B3				
N ₁ -H _{1n} ...O ₁	0.86	1.83	2.684(4)	171
C ₁ -H ₁ ...O ₃	0.93	2.52	3.381(4)	154
C ₂ -H ₂ ...O ₅	0.93	2.36	3.243(5)	158
C ₄ -H ₄ ...O ₆	0.93	2.39	3.264(5)	157
C ₅ -H ₅ ...O ₂	0.93	2.58	3.323(5)	137
O ₂ -H _{2p} ...O ₃	0.82	2.06	2.627(3)	126
O ₄ -H _{4p} ...O ₁	0.82	1.92	2.591(3)	139
O ₅ -H _{5p} ...O ₅	0.82	1.74	2.551(3)	168
O ₆ -H _{6p} ...O ₃	0.82	1.80	2.578(3)	160

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