Electronic Supplementary Material (ESI) for CrystEngComm

Supporting Information for

Synthon preference in O-protonated amide crystals – dominance of short strong hydrogen bonds

Sathyanarayana Reddy Perumalla and Changquan Calvin Sun*

Department of Pharmaceutics, College of Pharmacy, University of Minnesota, 308 Harvard Street S.E. Minneapolis, MN 55455 (USA), Fax: (+1) 612-626-2125

Table S1. Key properties of the reported amide salts.

Table S2. Crystallographic details for the new amide salts **1**-**12**.

Table S3. Key properties of the new amide salts **1-12**.

Table S1. Key properties of the reported amide salts.

	Refcode	Synthon	Interaction	D···A (Å)	Amide pK_a[e]	Acid pK_a[f]	ΔpKa	C=O distance (Å)[**]
Primary amides								
1	ACAMBR01	HB4	O···O	2.480	-0.47	-9 (HBr)	8.53	1.274
2	ACAMCL	HB4	O···O	2.450	-0.47	-7 (HCl)	6.53	1.265
3	BZAMTI01	HB4	O···O	2.407 and 2.422	-1.54	< -9.3 (HI_3)	7.76	1.271 & 1.274
4	FAMXIA	HB4	O···O	2.430	-0.47	-1.3 (HNO_3)	0.83	1.271 & 1.268
5	HEKYAX	HB3	O···Cl	2.889	-0.47	-7 (HCl)	6.53	1.298
6	HIRLIE	HB4	O···O	2.448	NA	~-3 (H_2SO_4)	NA	1.283
7	MACMNO	HB3	O···O[a]	2.566	-0.47	-1.3 (HNO_3)	0.83	1.287
8	RAFYIG	HB3	O···N	2.613	-0.53	NA (Te chloride salt)	NA	1.285
9	SUCABT	HB4	O···O[d]	2.451	-0.29 and -1.02	NA (Te bromide salt)	NA	1.263
10	VAYLAI	HB4	O···O	2.495	-0.47	-1.3 (HNO_3)	0.83	1.279
11	VOCPUY	HB3	O···O[c]	2.511	-1.54	-8 ($HClO_4$)	6.46	1.287
12	WUFMIU	HB3	O···Cl	3.326	-0.47	NA (Cu complex)	NA	1.313
Secondary amides								
1	AFEGAT	HB10	O···O[c]	2.446	-1.48	-7 (HCl)	5.52	1.272
2	BOPDUF	HB9	O···O	2.434	1.42	< -9.3 (H_2I_4)	>10.72	1.283
3	BOZGAY	HB9	O···O	2.435	-0.44	-7 (HCl)	6.56	1.268 & 1.269
4	CAPINC	HB9	O···O	2.432	-0.08	-7 (HCl)	6.92	1.275
5	CAPRLC	HB7	O···Cl	2.879	-0.14	-7 (HCl)	6.84	1.299 & 1.303
6	CUGMOG	HB10	O···O[a]	2.636	1.58	-3 (H_2SO_4)	1.42	1.293 & 1.302
7	CUJKEX	HB9	O···O	2.410	-0.44	NA (Ag complex)	NA	1.272 & 1.305
8	EGAKUS	HB10	O···O[a]	2.51	-1.66	~-3 (R-SO_3H)	1.34	1.299
9	ENANLC	HB7	O···Cl	2.922	-0.14	-7 (HCl)	6.86	1.307
10	FAJHUT	HB8	O···O	2.448	0.06	< -9 (HBr_3)	> 9.06	1.287
11	GEMQUM	HB8	O···O	2.44	-0.14	NA (Cr complex)	NA	1.277 & 1.276
12	GETMUO	HB8	O···O	2.427 and 2.437	-0.14	NA (Cr complex)	NA	1.284
13	HIQSIJ	HB9	O···O	2.406	0.12	-7(HCl)	7.12	1.286 & 1.268
14	JIJRUP	HB9	O···O	2.424	1.19	-1.3 (HNO_3)	2.49	1.268
15	LATBUF	HB10	O···O[c]	2.50	1.72	-7 (HCl)	8.72	1.290
16	LATSOQ	HB7	O···O[c]	2.41	-0.76	-7 (HCl)	6.24	1.277
17	MEDNOA	HB10	O···O[c]	2.51	-0.63	-9 (HBr)	8.37	1.290
18	MIJTAB	HB9	O···O[d]	2.453	-1.9	-3 (H_2SO_4)	1.1	1.272 & 1.270
19	PELAHC	HB9	O···O	2.432	-0.08	-7 (HCl)	6.92	1.275
20	PHACHI10	HB9	O···O	2.464	1.42	< -9.3 (HI_3)	>10.72	1.254
21	SADTUO	HB7	O···O[a]	2.45	-0.14	-1.72	1.58	1.277
22	SOYQED	HB10	O···O[a]	2.463	-0.53	-2.6	2.07	1.294
23	VALSUX	HB10	O···Cl	2.86	-0.64	-7 (HCl)	6.36	1.289
24	VOPXOO	HB10	O···O[b, d]	2.530	-0.81	-8 ($HClO_4$)	7.19	1.283
25	VOPXUU	HB10	O···O[b, d]	2.577	-1.17	-8 ($HClO_4$)	6.83	1.282
26	VOPYAB	HB10	O···O[b, d]	2.593	-1.17	-8 ($HClO_4$)	6.83	1.289
27	VOPYEF	HB10	O···O[c]	2.413	-1.17	-8 ($HClO_4$)	6.83	1.271
28	VOPYIJ	HB10	O···O[b, d]	2.522	-0.87	-8 ($HClO_4$)	7.13	1.291
29	VOPYOP	HB10	O···O[b, d]	2.647	-0.81	-8 ($HClO_4$)	7.19	1.325
30	VOPZIK	HB10	O···O[b, d]	2.572	-0.90	-8 ($HClO_4$)	7.10	1.293
31	VOPZOQ	HB10	O···O[b, d]	2.567	-0.80	-8 ($HClO_4$)	7.20	1.290
32	XAYGOV	HB9	O···O	2.43	1.72	-7 (HCl)	8.72	1.276 & 1.268
33	XIZQAY	HB9	O···O	2.440	-0.56	-7 (HCl)	6.44	1.282 & 1.272
34	ZAQMEL	HB9	O···O	2.44	-0.44	-9 (HBr)	8.56	1.278
Tertiary amides								
1	AWIQUS	HB11	O···O	2.436	-0.41	NA (Mo complex)	NA	1.271
2	BALNEH10	HB11	O···O	2.39	-0.41	NA (Re complex)	NA	1.310 & 1.302
3	CIXRIK	HB11	O···O	2.442	-0.44	NA (Te complex)	NA	1.269
4	ECAXUD	HB11	O···O	2.42	-0.41	NA (Te complex)	NA	1.280 (disorder)
5	ETIBUE	HB11	O···O[d]	2.405	-1.6	-9 (HBr)	7.4	1.281
6	FUNREM	HB11	O···O	2.438	-0.44	NA (-P complex)	NA	1.283
7	FUSWUL	HB11	O···O[d]	2.433	0.66	NA (Fe complex)	NA	1.296
8	FUVMUE	HB12	O···O[a]	2.564 and 2.584	-0.82	-3.91(TFMSA)	3.09	1.308 & 1.305
9	HDMAAU01	HB11	O···O	2.432	-0.41	NA (Au complex)	NA	1.276
10	HQUOAS	HB12	O···O[a]	2.495	0.49	NA (As complex)	NA	1.311
11	ILUNBR	HB12	O···O[c]	2.412 and 2.476	1.07	-9 (HBr)	10.07	1.321
12	JIJRID	HB11	O···O	2.431	-0.41	NA (Re complex)	NA	1.351
13	JINNEZ	HB11	O···O	2.414	0.44	NA (W, V complex)	NA	1.240
14	KENWUV	HB11	O···O	2.431	0.44	NA (Ag,Cu complex)	NA	1.258
15	KENXAC	HB11	O···O	2.389	-0.44	NA (Ag complex)	NA	1.250
16	KENXEG	HB11	O···O	2.364	-0.44	NA (Ag complex)	NA	1.224
17	KENXIK	HB11	O···O	2.423	-0.44	NA (Cu complex)	NA	1.255
18	KENXUW	HB11	O···O	2.353	-0.44	NA (Cu complex)	NA	1.258
19	KENYAD	HB11	O···O	2.425	-0.44	NA (Cu complex)	NA	1.243
20	MACMHC	HB12	O···Cl	2.869	-0.41	-7 (HCl)	6.59	1.304

21	MIVJUW	HB11	O···O	2.414	-0.41	< -9 (HBr_3)	8.59	1.271
22	MODSEE	HB12	O···O [a]	2.54	-0.41	-3 (H_2SO_4)	2.59	1.288
23	MQUOFA	HB11	O···O	2.43	0.49	NA ($HAsF_6$)	NA	1.280
24	OCOQOM	HB11	O···O	2.440	-0.41	NA (Thiophosphoramide complex)	NA	1.287
25	PILFEW	HB12	O···Cl	2.83	-0.41	-7 (HCl)	6.59	1.297
26	QECCUY	HB11	O···O	2.44	-0.41	NA (Mo complex)	NA	1.271, 1.284, 1.273, 1.242 & 1.310
27	QOMTER	HB12	O···O [a]	2.54	-1.28	-3.91(TFMSA)	2.63	1.306
28	RECFAM	HB11	O···O	2.387	-0.44	NA (Re complex)	NA	1.262
29	RIMQAF	HB11	O···O [d]	2.39 and 2.40	-0.49	NA (Co complex)	NA	1.283 & 1.313
30	SEGMOG01	HB11	O···O	2.522	-0.41	< -9 (HBr_3)	>8.59	1.257
31	SOJDOK	HB12	O···O=P	2.481	-0.41	NA (Tc complex)	NA	1.286
32	TAHGOY	HB12	O···Cl	2.82	-0.41	-7 (HCl)	6.59	1.283
33	VEQMOV	HB12	O···Cl	2.86	-0.41	-7 (HCl)	6.59	1.296
34	TIZFAJ	HB12	O···Cl	2.83	-1.34	-7 (HCl)	5.66	1.297
35	XULNEX	HB12	O···Cl	2.88	-1.01	-7 (HCl)	5.99	1.292

[a] oxygen of an anion, [b] oxygen of a crown ether; [c] oxygen of water; [d] intramolecular H-bonds. [e] pK_a values are obtained either calculated using ACD/pK_a (V 11.02)[1] or from various resources[2,3].
[f] Based on Mogul (v1.5) from CSD,[4] average C=O bond length in neutral amides is 1.244(13), 1.226(16), 1.225(20) for primary, secondary, and tertiary amides, respectively. C=O bond length in the identified amide salts are longer than the expected average for non-protonated amides.

Table S2. Crystallographic details for the new amide salts **1**-**12**.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
CCDC deposition number	**947738**	**947739**	**947740**	**947741**	**947742**	**947743**	**947744**	**947745**
Empirical formula	$C_9H_{12}Cl_1N_1O_2$	$C_9H_{12}Br_1N_1O_2$	$C_7H_8Cl_1N_1O_2$	$C_{54}H_{57}N_{15}O_{37}$	$C_9H_{12}Cl_1N_1O_6$	$C_7H_8N_2O_5$	$C_9H_{12}Cl_1N_1O_6$	$C_8H_{12}Br_1N_1O_3$
Formula wt.	201.65	246.11	173.59	1508.15	265.65	200.15	265.65	250.10
Crystal system	Monoclinic	Monoclinic	Monoclinic	Hexagonal	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)/c	P2(1)/c	P2(1)/c	R3	P2(1)/c	P2(1)/c	P2(1)/c	P2(1)/c
a [Å]	7.5611(6)	7.6316(6)	9.0833(6)	38.522(5)	6.7925(17)	10.2073(7)	6.7925(17)	5.8473(4)
b [Å]	14.9501(11)	15.2521(11)	5.1811(4)	38.522(5)	14.670(4)	5.0535(3)	14.670(4)	23.1474(15)
c [Å]	10.3894(6)	10.6249(6)	16.3294(11)	3.9027(5)	11.674(3)	16.9090(11)	11.674(3)	7.2982(5)
α [deg]	90	90	90	90	90	90	90	90
β [deg]	123.740(4)	124.184(4)	91.0110(10)	90	95.785(3)	104.7910(10)	95.785(3)	95.9480(10)
γ [deg]	90	90	90	120	90	90	90	90
Z	4	4	4	3	4	4	4	4
Volume [$Å^3$]	976.60(12)	1023.06(12)	768.37(9)	5015.6(12)	1157.4(5)	843.31(9)	1157.4(5)	982.49(11)
D_{calc} [g/cm^3]	1.371	1.598	1.501	1.498	1.525	1.576	1.525	1.691
F (000)	424	496	360	2346	552	416	552	504
μ [mm^{-1}]	0.358	3.986	0.442	0.129	0.347	0.136	0.347	4.159
$2\theta_{max.}$	27.14	27.49	27.31	27.39	27.38	27.30	27.38	27.53
Range h	-9<=h<=9	$-9 \le h \le 9$	11<=h<=11	-49<=h<=49	-8<=h<=8	-13<=h<=13	-8<=h<=8	-7<=h<=7
Range k	-19<=k<=19	$-19 \le k \le 19$	-6<=k<=6	-49<=k<=49	0<=k<=18	-6<=k<=6	0<=k<=18	-29<=k<=29
Range l	-13<=l<=13	$-13 \le l \le 13$	-20<=l<=21	-5<=l<=5	0<=l<=15	-21<=l<=21	0<=l<=15	-9<=l<=9
N-total	10823	11566	8245	19178	2594	8523	8748	11212
N-independent	2168	2330	1733	4982	2594	1901	2123	2268
N-observed	1998	2028	1497	3734	2334	1662	1715	1963
R_1 [I>2σ(I)]	0.0257	0.0210	0.0275	0.0650	0.0330	0.0322	0.0338	0.0271
wR_2	0.0729	0.0508	0.0794	0.2149	0.0869	0.0893	0.0882	0.0619
GOF	1.061	1.038	1.095	1.517	1.056	1.077	1.058	1.078

	9	**10**	**11**	**12**
CCDC deposition number	**947746**	**947747**	**947748**	**947749**
Empirical formula	$C_{20}H_{27}Cl_1N_2O_4$	$C_{20}H_{33}Cl_2N_2O_7$	$C_{40}H_{54}Br_2N_4O_8$	$C_{20}H_{33}Br_2N_2O_7$
Formula wt.	394.89	484.38	878.69	573.30
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	C2/c	P-1	P21/c	P-1
a [Å]	26.813(5)	6.7923(4)	13.3000(7)	6.8379(8)
b [Å]	5.6138(11)	13.4759(8)	12.1554(7)	13.7200(16)
c [Å]	13.838(3)	14.1913(8)	28.5010(14)	14.2131(17)
α [deg]	90	76.1270(10)	90	76.208(2)
β [deg]	90.014(2)	77.3120(10)	111.742(2)	77.572(2)
γ [deg]	90	87.9620(10)	90	87.122(2)
Z	4	2	4	2
Volume [$Å^3$]	2082.9(7)	1230.08(12)	4279.9(4)	1264.6(3)
D_{calc} [g/cm^3]	1.259	1.308	1.364	1.506
F (000)	840	514	1824	586
μ [mm^{-1}]	0.210	0.305	1.947	3.245
$2\theta_{max.}$	27.57	27.63	27.45	26.71
Range h	-34<=h<=34	-8<=h<=8	-17<=h<=17	-8<=h<=8
Range k	-7<=k<=7	-17<=k<=17	-15<=k<=15	-17<=k<=17
Range l	-17<=l<=18	-18<=l<=18	-36<=l<=36	-17<=l<=17
N-total	11859	14262	48114	13797
N-independent	2384	5614	9746	5297
N-observed	2318	4454	7848	4457
R_1 [I>2σ(I)]	0.0327	0.0508	0.0285	0.0331
wR_2	0.1077	0.1835	0.0717	0.0969
GOF	1.105	1.315	1.008	1.042

Table S3. Key properties of the new amide salts **1-12**.

Structure code	**Synthon**	**Interaction**	**D···A (Å)**	**Amide pK_a**	**Acid pK_a**	**ΔpK_a**	**C=O distances** (Å)
1	HB2	O···Cl	2.86	-1.18	-7 (HCl)	5.82	1.298
2	HB2	O···Br	3.05	-1.18	-9 (HBr)	7.82	1.300
3	HB2	O···Cl	2.94	-1.08	-7 (HCl)	5.92	1.303
4	HB1	O···O^a	2.40	-1.18	-1.3 (HNO_3)	0.22	1.278 & 1.254
5	HB1	O···O^a	2.58	-1.18	-8 ($HClO_4$)	6.82	1.306
6	HB1	O···O^a	2.62	-1.08	-1.3 (HNO_3)	0.22	1.309
7	HB1	O···O^a	2.68	-1.08	-8 ($HClO_4$)	6.92	1.305
8	HB10	O···O^a	2.50	1.72	-9 (HBr)	10.72	1.283
9	HB9	O···O	2.44	1.42	-7 (HCl)	8.42	1.263
10	HB9	O···O	2.42	1.42	-7 (HCl)	8.42	1.276
11	HB9	O···O	2.43 & 2.44	1.42	-9 (HBr)	10.42	1.265 & 1.267
12	HB9	O···O	2.42	1.42	-9 (HBr)	10.42	1.265

References:

(1) http://www.acdlabs.com/products/percepta/predictors/pka/.
(2) http://www.ochemonline.com/PKa_data.
(3) Lundblad, R. L.; Macdonald, F. M. In *Handbook of Biochemistry and Molecular Biology (Fourth Edition)*; Fourth ed.; CRC Press: 2010, p 537.
(4) http://www.ccdc.cam.ac.uk/Solutions/CSDSystem/Pages/Mogul.aspx.