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'Masked synthons' in crystal engineering: insulated components in acetaminophen cocrystal hydrates

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Supplementary Information

Experimental

1. Crystallographic studies

Single crystals of **1**-**4** were individually mounted on a glass fiber. Intensity data were collected on a Bruker APEX2 system. Data were collected at 100 K with graphite-monochromated MoK_α radiation (λ = 0.71073 Å). Data were collected in four sets using omega-phi scans with omega steps of 0.5° and phi steps of 90°. A total of 1464 frames were collected. Data were processed using SaintPlus.[1] Corrections for Lorentz-polarisation effects were applied. Absorption was negligible. All structures were solved using direct methods that yielded the non-hydrogen atoms. All hydrogen atoms were located in Fourier-difference electron density maps. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained riding positions. Hydrogen atoms associated with oxygen atoms were included in the located positions. Refinement was achieved with the use of SHELX-97.[2] Structure **1** contains a one half BPE molecule that lies on a center of inversion and is unequally disordered over two orientations. In addition, a single water molecule is unequally disordered over two positions, yet, maintains the same hydrogen bonding interactions. The crystallographic data for **1**-**4** are summarised in Table 1.

Table S1. Crystallographic parameters for structures **1-4**.

	1	**2**	**3**	**4**
Chem. formula	$(C_8H_9O_2N)\cdot 1.5(C_{12}H_{10}N_2)\cdot 4(H_2O)$	$(C_8H_9O_2N)\cdot 1.5(C_{12}H_{10}N_2)\cdot 2(H_2O)$	$(C_8H_9O_2N)\cdot (C_{12}H_{10}N_2)\cdot 2(H_2O)$	$(C_{12}H_{10}N_2)\cdot 2(C_8H_9O_2N)\cdot (C_2H_6O)$
M_r	496.56	460.52	369.41	530.61
Crystal system	triclinic	triclinic	monoclinic	triclinic
a/Å	8.4243(14)	9.2028(9)	6.5584(5)	8.835(3)
b/Å	12.227(2)	11.5290(12)	40.426(3)	10.724(3)
c/Å	13.193(2)	11.7206(12)	7.1631(5)	15.174(4)
α/°	96.960(2)	93.3410(10)	90.00	91.638(4)
β/°	93.427(2)	99.5260(10)	97.5890(10)	100.515(4)
γ/°	101.280(2)	102.8040(10)	90.00	106.191(4)
V/Å^3	1318.0(4)	1190.1(2)	1882.5(2)	1352.6(7)
T/K	100(2)	100(2)	100(2)	100(2)
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
Z	2	2	4	2
Radiation type	MoK_α	MoK_α	MoK_α	MoK_α
θ range	1.56 to 27.55	1.77 to 27.57	2.02 to 27.50	1.98 to 27.49
μ/mm^{-1}	0.090	0.088	0.092	0.090
D_c/gcm^{-3}	1.251	1.285	1.303	1.303
No. refl. measured	15528	13902	21710	15926
No. indep. refl.	5980	5375	4326	6122
R_{int}	0.0388	0.0154	0.0208	0.1800
R_1 ($I > 2\sigma(I)$)	0.0370	0.0358	0.0411	0.0625
$wR(F^2)$ ($I > 2\sigma(I)$)	0.1150	0.1322	0.1265	0.1653
R_1 (all data)	0.0443	0.0413	0.0470	0.0715
$wR(F^2)$ (all data)	0.1250	0.1398	0.1330	0.1757
GooF on F^2	0.878	1.181	0.878	1.053
CCDC number	889476	889477	889478	889479

Table S2. Selected hydrogen-bond parameters for **1-4**.

Cocrystal	*D*–H···*A*	*D*–H	*d*(H···*A*) / Å	*d*(*D*···*A*) / Å	*θ*(*D*–H···*A*) / º
1	N1–H1···O3′	0.86	2.02	2.827 (7)	157
	N1–H1···O3	0.86	1.91	2.765 (6)	175
	O1–H1O···O5^{ii}	0.922 (18)	1.698 (18)	2.6195 (11)	177.8 (15)
	O5–H5OB···O2	0.88 (1)	1.83 (1)	2.7066 (12)	174 (1)
	O5–H5OA···O6	0.89 (1)	1.84 (1)	2.7323 (12)	176 (2)
	O6–H6OA···N2	0.90 (1)	1.88 (1)	2.7737 (13)	173 (1)
	O4–H4OA···O6^{iii}	0.89 (1)	1.92 (1)	2.7947 (12)	168 (2)
	O4–H4OB···N3^{i}	0.88 (1)	1.86 (1)	2.7426 (13)	177 (2)
	O6–H6OB···O4^{iv}	0.89 (1)	1.87 (1)	2.7495 (13)	168 (2)
	O3′–H3OC···O4	0.88 (1)	1.97 (3)	2.807 (5)	159 (7)
	O3′–H3OD···N4′	0.88 (1)	2.03 (4)	2.88 (2)	162 (11)
	O3′–H3OD···N4	0.88 (1)	2.00 (5)	2.837 (8)	158 (12)
	O3–H3OA···O4	0.88 (1)	1.90 (2)	2.750 (5)	161 (3)
	O3–H3OB···N4′	0.88 (1)	2.03 (3)	2.82 (2)	147 (3)
	O3–H3OB···N4	0.88 (1)	2.00 (2)	2.819 (8)	153 (3)
2	O1–H1O···O3^{v}	0.82	1.79	2.6030 (11)	171
	N1–H1···O4	0.86	1.97	2.8193 (11)	168
	O3–H3A···N4	0.87 (1)	1.94 (1)	2.7969 (12)	168 (2)
	O3–H3B···O2	0.88 (1)	1.86 (1)	2.7216 (10)	167 (1)
	O4–H4A···N2	0.88 (1)	1.93 (1)	2.8022 (12)	169 (2)
	O4–H4B···O1^{vi}	0.88 (1)	2.00 (1)	2.8854 (10)	178 (1)
3	O4–H4B···O3	0.97 (4)	1.85 (4)	2.8148 (15)	171 (3)
	O4–H4A···N3^{vii}	0.86 (2)	1.99 (2)	2.8395 (16)	172 (2)
	O3–H3B···O4^{viii}	1.00 (4)	1.83 (4)	2.8104 (15)	166 (4)
	O3–H3A···O2^{ix}	0.88 (2)	1.85 (2)	2.7261 (14)	176 (2)
	N1–H1···O3	0.86	2.02	2.8743 (14)	176
	O1–H1O···N2	0.93 (2)	1.78 (2)	2.7135 (15)	173 (2)
4	O5–H5O···O4	0.87 (3)	1.93 (3)	2.7841 (18)	167 (2)
	O3–H3O···N4^{x}	0.99 (3)	1.72 (3)	2.7040 (18)	172 (2)
	O1–H1O···N3	0.96 (2)	1.82 (2)	2.7726 (18)	175 (2)
	N2–H2N···O2	0.86	2.05	2.8867 (17)	165
	N1–H1···O5^{xi}	0.86	2.06	2.9104 (18)	170

Symmetry codes : (i) −x+1, −y+1, −z+2; (ii) −x, −y+1, −z; (iii) x, y−1, z; (iv) −x, −y+1, −z+1 ; (v) −x+2, −y+2, −z+3; (vi) −x+2, −y+1, −z+3 ; (vii) −x, y−1/2, −z+1/2; (viii) −x+2, −y, −z+1; (ix) x+1, y, z ; (x) −x−1, −y+1, −z+1; (xi) x+1, y+1, z.

2. Cambridge Structural Database analysis

The survey of the CSD (version 5.32, update 5, November 2011) was performed with ConQuest30 (version 1.13) to investigate cocrystal hydrates. The structures were targeted to satisfy the following criteria: (a) crystallographic R factor < 0.10, (b) no ions, (c) 3D coordinates fully determined, (d) and purely organic components.[3] A search for entries that contain the structure H-O-H retrieved molecular hydrates. The results were refined to those entries that contain 3, 4, 5, or 6 chemical units. The entries were individually examined for solids containing at least two components that are solids at ambient conditions. Within the remaining entries, a cocrystal was deemed to contain masked synthons when the components comprise functionalities capable of assembling into supramolecular synthons but lack direct hydrogen bonding. The hydrogen bonding interactions between components were limited to those interactions less than the sum of the van der Waals radii.[4] For masked synthons comparable to **1**-**4**, we excluded host-guest/clathrate systems and structures formed in the strict absence of crystal engineering precepts. Table S3 contains CSD reference codes and corresponding literature references for cocrystal hydrates that exhibit masked synthons. Table S4 contains CSD reference codes and corresponding literature references for cocrystals that exhibit complete synthon success in addition to cocrystal hydrates.

Table S3. CSD codes and citations to hydrated cocrystals with masked synthons.

Entry	CSD Reference Code	Reference
1	MAHKEN	D. Braga, F. Grepioni, L. Maini, P. P. Mazzeo and K. Rubini, *Thermochim. Acta*, 2010, **507**, 1.
2	AJEZAR	A. Czapik and M. Gdaniec, *Acta Crystallogr., E: Struct. Rep. Online*, 2009, **65**, O3177.
3	CUWKAG	M. Y. Antipin, A. I. Akhmedov, Y. T. Struchkov, E. I. Matrosov and M. I. Kabachnik, *J. Struct. Chem.*, 1983, **24**, 888.
4	EVAFIR	M. F. Wang, *Acta Crystallogr., E: Struct. Rep. Online*, 2011, **67**, O1581.
5	FEZQOR	M. Ueda, T. Mochida, S. Furukawa, H. Suzuki, H. Moriyama and H. Mori, *Mol. Cryst. Liq. Cryst.*, 2002, **379**, 153.
6	HOMXUC	G. Buczak, Z. Dega-Szafran, A. Katrusiak and M. Szafran, *J. Mol. Struct.*, 1997, **437**, 143.
7	IBUXUZ	J. PrakashaReddy and V. R. Pedireddi, *Tetrahedron*, 2004, **60**, 8817.
8	IBUYEK	J. PrakashaReddy and V. R. Pedireddi, *Tetrahedron*, 2004, **60**, 8817.
9	NUDMII	G. Smith, D. E. Lynch, K. A. Byriel and C. H. L. Kennard, *Z. Kristallogr.*, 1997, **212**, 130.
10	UFENAY	K. A. Al-Farhan, *J. Saudi Chem. Soc.*, 2000, **4**, 169.
11	WUVKII	M. L. Cheney, N. Shan, E. R. Healey, M. Hanna, L. Wojtas, M. J. Zaworotko, V. Sava, S. J. Song and J. R. Sanchez-Ramos, *Cryst. Growth Des.*, 2010, **10**, 394.
12	TIKPAF	M. Rafilovich, J. Bernstein, M. B. Hickey and M. Tauber, *Cryst. Growth Des.*, 2007, **7**, 1777.
13	AKAVIR	V. R. Pedireddi and J. PrakashaReddy, *Tetrahedron Lett.*, 2003, **44**, 6679.
14	HOPJUS	K. K. Arora, M. S. Talwelkar and V. R. Pedireddi, *New J. Chem.*, 2009, **33**, 57.
15	IPEWAC	A. Lemmerer, *Acta Crystallogr., B: Struct. Sci.*, 2011, **67**, 177.
16	ITOCAV	D. E. Turkington, A. J. Lough, G. Ferguson and C. Glidewell, *Acta Crystallogr., B: Struct. Sci.*, 2004, **60**, 238.
17	KIZXEW	D. E. Lynch, G. Smith, K. A. Byriel and C. H. L. Kennard, *Aust. J. Chem.*, 1991, **44**, 1017.
18	NEWXOC	B. M. Kariuki, K. D. M. Harris, D. Philp and J. M. A. Robinson, *J. Am. Chem. Soc.*, 1997, **119**, 12679.
29	NUDMUU	G. Smith, D. E. Lynch, K. A. Byriel and C. H. L. Kennard, *Z. Kristallogr.*, 1997, **212**, 130.
20	OGAHIN	V. S. Senthil Kumar, A. Nangia, A. K. Katz and H. L. Carrell, *Cryst. Growth Des.*, 2002, **2**, 313.
21	QANMEY	T. R. Sarangarajan, K. Panchanatheswaran, J. N. Low and C. Glidewell, *Acta Crystallogr., C: Cryst. Struct. Commun.*, 2005, **61**, O118.
22	UHAHUG	D. Britton and M. K. Chantooni, *J. Chem. Crystallogr.*, 2001, **31**, 5.
23	UHAJAO	D. Britton and M. K. Chantooni, *J. Chem. Crystallogr.*, 2001, **31**, 5.
24	YAXCEF01	M. K. Chantooni, D. Britton and I. M. Kolthoff, *J. Cryst. Spectrosc.*, 1993, **23**, 497.
25	ODEBUV	Z. L. Wang, M. X. Li, L. H. Wei and J. P. Wang, *Acta Crystallogr., E: Struct. Rep. Online*, 2006, **62**, O2508.
26	SETQUE	T. Lavy, N. Meirovich, H. A. Sparkes, J. A. K. Howard and M. Kaftory, *Acta Crystallogr., C: Cryst. Struct. Commun.*, 2007, **63**, O89.
27	VEVLIS	G. Smith, U. D. Wermuth, P. C. Healy and D. J. Young, *J. Chem. Crystallogr.*, 2006, **36**, 805.
28	BUJWIN	H. Hadadzadeh, A. R. Rezvani, M. K. Abdolmaleki, K. Ghasemi, H. Esfandiari and M. Daryanavard, *J. Chem. Crystallogr.*, 2010, **40**, 48.
29	EBAWEK	B. Zaman, K. A. Udachin and J. A. Ripmeester, *Cryst. Growth Des.*, 2004, **4**, 585.
30	EBAWAG	B. Zaman, K. A. Udachin and J. A. Ripmeester, *Cryst. Growth Des.*, 2004, **4**, 585.

Table S4. CSD ref codes and citations to cocrystals with synthon success and hydrates.

Entry	CSD Reference Code	Reference
1	CUWJUZ	M. Y. Antipin, A. I. Akhmedov, Y. T. Struchkov, E. I. Matrosov and M. I. Kabachnik, *J. Struct. Chem.*, 1983, **24**, 888.
2	HOMXOW	G. Buczak, Z. Dega-Szafran, A. Katrusiak and M. Szafran, *J. Mol. Struct.*, 1997, **437**, 143.
3	MACCID	K. F. Bowes, G. Ferguson, A. J. Lough and C. Glidewell, *Acta Crystallogr., B: Struct. Sci.*, 2003, **59**, 277.
4	ZOKYON	M. K. Chantooni and D. Britton, *J. Chem. Crystallogr.*, 1995, **25**, 351.
5	SETQOY	T. Lavy, N. Meirovich, H. A. Sparkes, J. A. K. Howard and M. Kaftory, *Acta Crystallogr., C: Cryst. Struct. Commun.*, 2007, **63**, O89.

3. References

1. *SaintPlus,* (1997-2003) Bruker AXS Inc., Madision, WI, USA.
2. G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112.
3. L. Infantes, J. Chisholm and S. Motherwell, *CrystEngComm*, 2003, **5**, 480.
4. A. L. Gillon, N. Feeder, R. J. Davey and R. Storey, *Cryst. Growth Des.*, 2003, **3**, 663.