Electronic Supplementary Material (ESI) for ChemComm.

Modulating physical properties of solid forms of urea using co-crystallization technology

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Supplementary information

Contents

1. Experimental

1.1 Materials

Urea and all co-formers were purchased from Aldrich and utilized without further purification. Melting points were measured using Fisher-Johns melting point apparatus. IR spectra were recorded with a Nicolet 380 FT-IR using ZnSe crystal.

1.2 Full interaction maps (FIMs) and CSD search

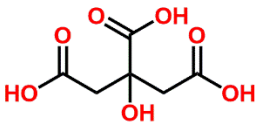
The first phase of this study involves the use of several complementary approaches pursued in parallel. In order to develop robust protocols for co-crystal synthesis of urea we combine a knowledge-based approach for mapping out the intermolecular interactions that are most likely to take place with the different parts of the urea functionality. To this end, a careful analysis of all relevant structural data from the Cambridge Crystallographic Data Centre will furnish a map of the most likely short contacts with the C=O and the N-H moieties. The data is analyzed using full interaction maps (FIMs) which provides 3-D maps of intermolecular interactions based upon existing experimental structural data.

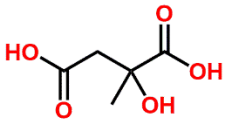
1.3 Co-crystal screening

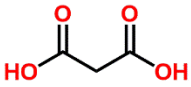
60 different co-formers were chosen based on FIMs search and urea was put through a co-crystal screen using liquid-assisted grinding (LAG) in a drop of methanol against 60 co-formers in stoichiometric amounts. The solid resulting from each reaction was characterized using IR spectroscopy to determine if a co-crystal had formed. A positive co-crystal outcome was considered when peaks from both urea and co-former were present in the grinded mixture and shifted more than 7 wavenumbers as well as the appearance of broad stretches around 2,300 and 1,800 cm^{-1} as a result of intermolecular O-H…N hydrogen bonds were taken as an indication of co-crystal formation (such hydrogen bonds would not be possible in either of the pure compounds).

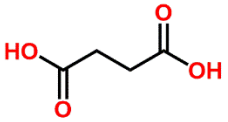
Scheme S1. List of co-formers used in this study.

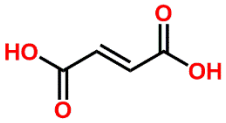
Aliphatic acids

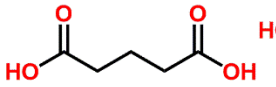

Citric acid (CA)

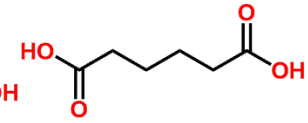

Citramalic acid (CmA)

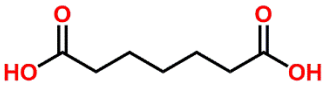

Malonic acid (MA)

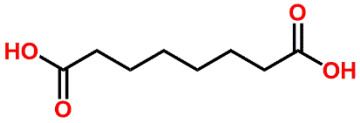

Succinic acid (SA)

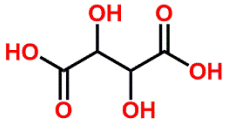

Fumaric acid (FA)

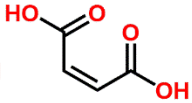

Glutaric acid (GA)

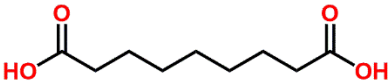

Adipic acid (AA)

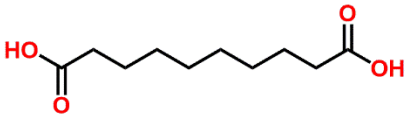

Pimelic acid (PA)


Suberic (SbA)

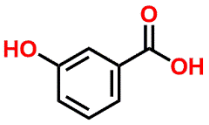

Tartaric acid (TA)

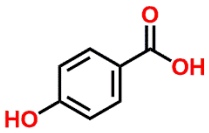

Maleic acid (MeA)

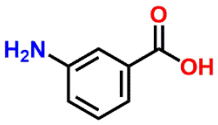

Azelaic acid (AzA)

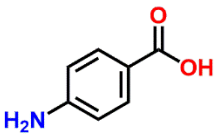

Sebacic acid (SeA)

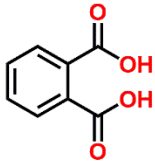
Aromatic acids

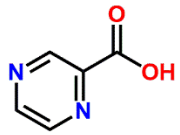

3-Hydroxy benzoic acid (3HBA)

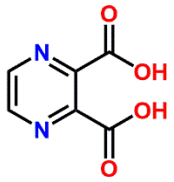

4-Hydroxy benzoic acid (4HBA)

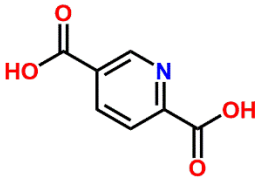

3-Amino benzoic acid (3ABA)

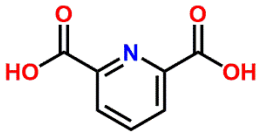

4-Amino benzoic acid (4ABA)

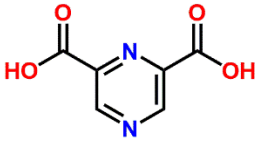

Phthalic acid (PtA)

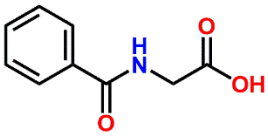

Pyrazine-2-carboxylic acid (Py2_CA)

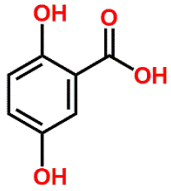

Pyrazine2,3-dicarboxylic acid (Py2, 3DCA)

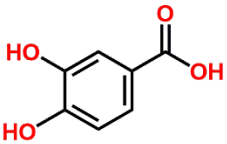

Pyridine2,5-dicarboxylic acid (P2, 5DCA)

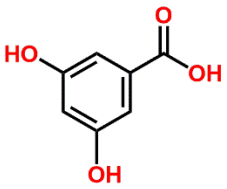

Pyridine 2,6-dicarboxylic acid (P2, 6DCA)


Pyrazine 3,5-dicarboxylic acid (Py3,5DCA)

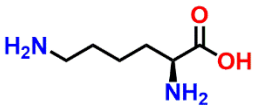

Hippuric acid (HipA)

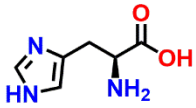

2,5-dihydroxybenzoic acid (2,5DHBA)

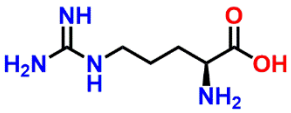

3,4-dihydroxybenzoic acid (3,4DHBA)

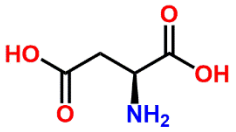

3,5-dihydroxybenzoic acid (3,5DHBA)

Amino acids


Lysine (Lys)

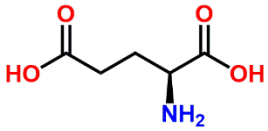

Histidine (His)

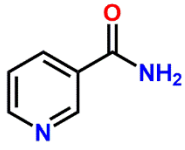

Arginine (Arg)

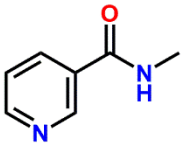

Aspartic acid (Asp)

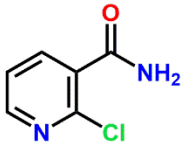

Alanine (Ala)

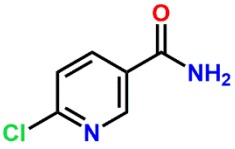
Nicotinamide's


Glutamic acid (Glu)


Nicotinamide (N)

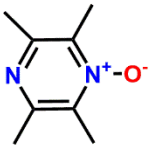

N-methyl-nicotinamide (Me_N)

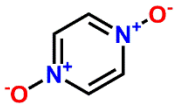

2-chloro-nicotinamide (2Cl_N)


6-chloro-nicotinamide (6Cl_N)

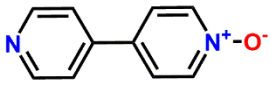
N-oxides


Pyrazine N-oxide (Py_NO)

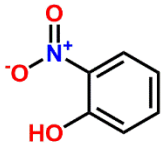

Tetramethyl pyrazine N-oxide (TmPy_NO)

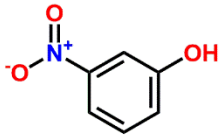

Pyrazine-NN-oxide (Py _NNO)

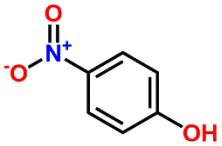

Tetramethylpyrazine-NNoxide (TmPy_NNO)


Bipyridine-N-oxide (BiP_NO)

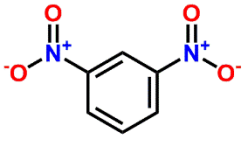
Nitro-subtituents

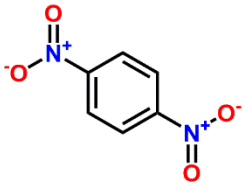

o-nitrophenol (2NP)


m-nitrophenol (3NP)

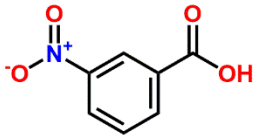

p-nitrophenol (4NP)

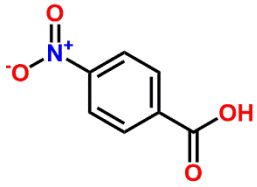

1,2-dinitrobenzene 1,2DNB


1,3-dinitrobenzene 1,3DNB

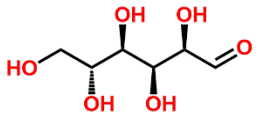

1,4-dinitrobenzene 1,4DNB


o-nitrobenzoic acid 2NBA

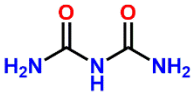

m-nitrobenzoic acid 3NBA


p-nitrobenzoic acid 4NBA

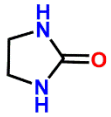
Various



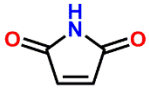
Glucose (Gl)



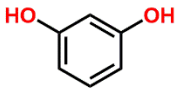
Biuret (Biu)



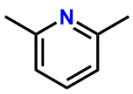
Imidazolidone (Im)



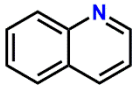
Maleimide (Ma)



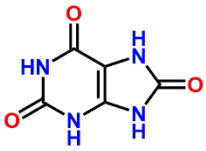
Resorcinol (Re)



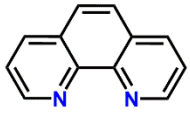
2,6-Lutidine (Lut)



Quinoline (Qui)



Uric acid (Ur)



1,10-Phenanthrolin (Phen)

1.4 Grinding experiment results

Table S1. Experimental outcome of grinding experiments based on IR for co-crystallizations of urea with co-formers. Co-formers with subscripts are already reported in the literature.

	Urea co-crystal	Outcome		Urea co-crystal	Outcome		Urea co-crystal	Outcome
	Aliphatic acids			**Aromatic acids**			**Nitro substituents**	
1	U:CA	✓	**14**	U:3HBA	✓	**28**	U:2NP	×
2	U:CmA	✓	**15**	U:4HBA	✓[1]	**29**	U:3NP	✓
3	U:MA	✓[2]	**16**	U:3ABA	×	**30**	U:4NP	✓[3, 4]
4	U:SA	✓[5,6,7]	**17**	U:4ABA	✓[8]	**31**	U:1,2DNB	✓
5	U:FA	✓[9, 10,6]	**18**	U:PtA	✓[8]	**32**	U:1,3DNB	✓
6	U:GA	✓[11, 12]	**19**	U:Py2_CA	✓	**33**	U:1,4DNB	✓
7	U:AA	✓[13]	**20**	U:Py2,3_DCA	✓[8]	**34**	U:2NBA	✓
8	U:PA	✓[14]	**21**	U:Py2,5_DCA	×	**35**	U:3NBA	✓[15]
9	U:SbA	✓	**22**	U:Py2,6_DCA	✓[8]	**36**	U:4NBA	✓
10	U:TA	✓[16, 17]	**23**	U:Py3,5_DCA	×			
11	U:MeA	✓[7]	**24**	U:HipA	×			
12	U:AzA	✓	**25**	U:2,5DHBA	✓[1]			
13	U:SeA	✓	**26**	U:3,4DHBA	✓			
			27	U:3,5DHBA	✓[1]			
	Amino acids			**Nicotinamides**			**N-oxides**	
37	U:Lys	✓	**43**	U:N	✓[18]	**47**	U:Py_NO	✓
38	U:His	✓	**44**	U:Me_N	✓	**48**	U:TmPy_NO	✓
39	U:Arg	✓	**45**	U:2Cl_N	×	**49**	U:Py_NNO	✓
40	U:Asp	×	**46**	U:6Cl_N	×	**50**	U:TmPy_NNO	✓
41	U:Ala	×				**51**	U:BiP_NO	✓
42	U:Glu	✓						
Various								

52	U:Gl	✓[19]	**57**	U:Lut	✓[20]			
53	U:Biu	×	**58**	U:Qui	✓[21]			
54	U:Im	✓[22]	**59**	U:Ur	×			
55	U:Ma	✓	**60**	U:Phen	✓[23]			
56	U:Re	✓[24]						

An example of analysis of IR grinding experiments using infra-red spectroscopy.

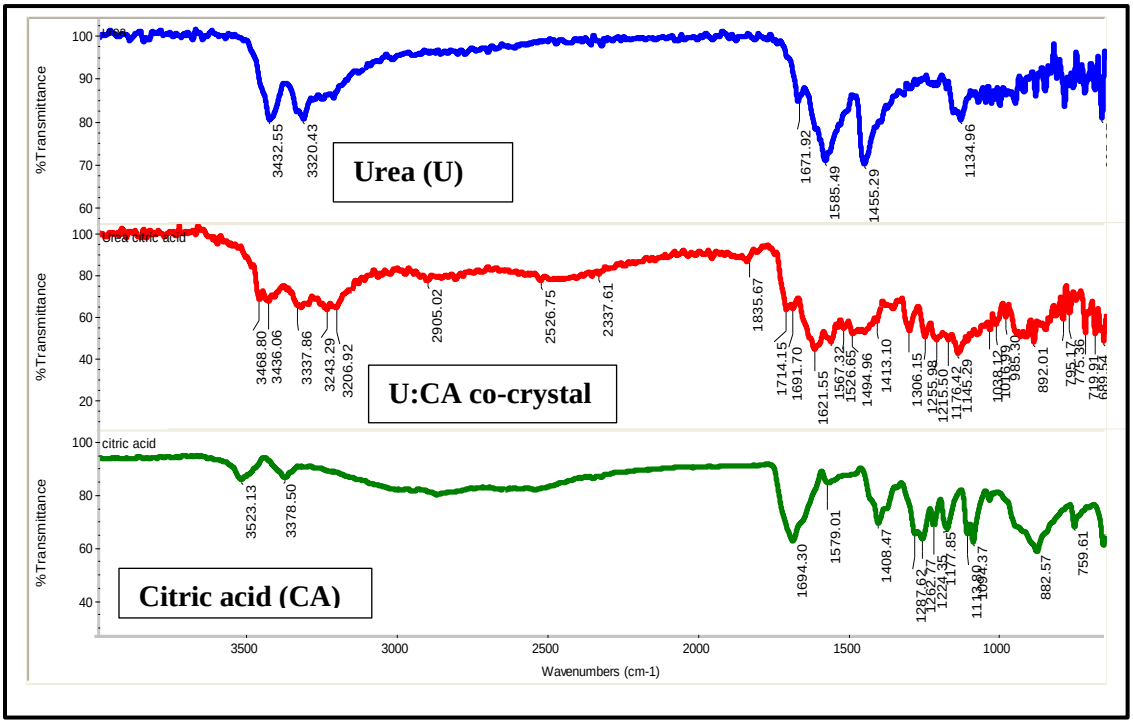


Figure S1. Examples of IR spectra for a successful co-crystallization: U(blue), U:CA (red) and CA (green).

1.5 IR analysis of liquid assisted grinding experiments.

Table S2. IR results of grinding experiments for co-crystallizations with aliphatic acids.

Urea	Co-former	Ground mixture	Results	Urea	Co-former	Ground mixture	Results
Urea	**CA**	**U:CA**		**Urea**	**CmA**	**U:CmA**	
1708, 1672	1694	1697		1708, 1672	1732	1701	
1587, 1555	1571	1569, 1527		1587, 1555	-	1611, 1554	
1455	1408	1427		1455	1471, 1426	1456	
-	1262	1258	**Co-crystal**	-	1369, 1325	1338, 1304	**Co-crystal**
1145, 1038	1113, 1094	1142, 1079		1145, 976	1189, 1115	1175, 1127	
976	-	951		1038	-	1024	
-	882	876			961	966	
Urea	**MA**	**U:MoA**		**Urea**	**SA**	**U:ScA**	
3429, 3333	2989, 2906	3456, 3198		3429, 3333	2956	3464, 3323	
2354		2487, 1857		2354		2373, 1908	
1708, 1672	1693	1658		1708, 1672	1678	1615	
1587	-	1580		1587	-	-	
1455	1433	1463, 1404	**Co-crystal**	1455	1410,	1459	**Co-crystal**
-	1300	-		-	1306	1326	
1145	1214, 1167	1291, 1162		1145	1197	1197	
976	916	935, 876		976	635	1005	
788, 699	767, 652	747		788, 699	-	906	
Urea	**FA**	**U:FA**		**Urea**	**GA**	**U:GA**	
3429, 3333		3472, 3218		3429, 3333		3325	
2354	2910, 2843	2362, 1869		2354	2911, 2823	2362, 1975	
1708, 1672	1686	1617		1708, 1672	1686	1701, 1623	
1587		1521		1587	1427	1575	
1455	1427, 1405	1460		1455	1332	1463	
-	1350	1300	**Co-crystal**	-	1279, 1222		**Co-crystal**
	1297, 1232	-		1145	1185	1138	
1145	1186	1146, 1013		976	922	970	
976	923	936		788, 699	680	782	
788, 699	676	773, 621					
Urea	**AA**	**U:AdA**		**Urea**	**PA**	**U:PA**	
3429, 3333	2950	3472, 3225		3429, 3333		3468, 3210	
2354		2389, 1898		2354	2911, 2823	2420, 1889	
1708, 1672	1683	1687, 1636		1708, 1672	1686	1693, 1658	
1587	1461	1563		1587	1427	1572	
1455	1406	1495	**Co-crystal**	1455	1332	1434, 1407	**Co-crystal**
-	1314	1338		-	1279, 1222	1349, 1264	
1145	1272, 1189	1258, 1182		1145	1185	1189, 1091	
976		971		976	922	976	
788,699	733	731, 680		788, 699	680	778, 615	
Urea	**SbA**	**U:SbA**		**Urea**	**AzA**	**U:AzA**	
3429, 3333		3338, 3203		3429, 3333		3464, 3222	
2354	2934, 2868	2353, 1818		2354	2911, 2823	2483, 1904	
1708, 1672	1684	1702, 1649		1708, 1672	1686	1786, 1657	
1587	1422, 1407	1592		1587	1427	1591, 1435	
1455	1330	1487	**Co-crystal**	1455	1332	1314	**Co-crystal**
-	1248	1331		-	1279, 1222	1242	
		1229		1145	1185	1162	
1145, 976	1187	1186		976	922	983, 904	
788, 699	922	953		788, 699	680	771, 613	
Urea	**TA**	**U:TA**		**Urea**	**MeA**	**U:MeA**	
1708	1736, 1716	1712		1708, 1672	1686	1709	
1587	-	1622		1587		1611	
1301,1252	1219	1300, 1233	**Co-crystal**	1455	1427, 1405	1463	**Co-crystal**
1038	1085	1098		-	1350	1396	
979	936	976		1145	1186	1194, 1110	
699	685	702		976	923	982	
Urea	**SeA**	**U:SeA**					
3429, 3333		3343, 3206					
2354	2910, 2843	1830					
1708, 1672	1686	1693, 1650	**Co-crystal**				
1587		1592					
1145	1186	1189					
976	923	919					

Table S3. IR results of grinding experiments for co-crystallizations with aromatic acids.

Urea	Co-former	Ground mixture	Results	Urea	Co-former	Ground mixture	Results
Urea	**3HBA**	**U:3HBA**		**Urea**	**4HBA**	**U:3HBA**	
3429, 3333	3350	3432, 3320	**Co-crystal**	3429, 3333	3368	3421, 3347	**Co-crystal**
2354		2589		2354		2502, 1893	
1708, 1672	1678	1702		1708, 1672	1668, 1606	1663, 1631	
1587	1594	1597		1587	1592	1584	
1455	1459	1452		1455	1446	1467	
-	1226	1269		-	1286	1374, 1254	
1145, 976		1157, 1106		1145, 976		1154	
788, 699	753	751		788, 699	767	841, 743	
Urea	**3ABA**	**U:3ABA**		**Urea**	**4-ABA**	**U:4ABA**	
3429	-	3429	**No Co-crystal**	3429, 3333	3460, 3355	3480, 3362	**Co-crystal**
1672	1622	1619		2354		2549, 1924	
-	1553	1533, 1514		1708, 1672	1658,1623	1618	
-	1386	1378		1587	1597	1588	
	1223	1217		1455	1420	1408	
1145	-	1138		-	1309	1313	
788	786, 757	786, 755		1145, 976	1285	1271, 1166	
699	666	673		788, 699	768	912, 837, 771	
Urea	**PtA**	**U:PtA**		**Urea**	**Py2_CA**	**U:Py2_CA**	
3429, 3333			**Co-crystal**	1672		1666	**Co-crystal**
2354	1667	1636		1587, 1455		1582, 1450	
1587	1583	1541			1386	1395	
1455	1399	1370			1309, 1270	1310, 1269	
1145	1268	1286		1145	1152	1152	
976				1038	1052	1049	
788, 699				715	715	715	
				699	698	690	
Urea	**Py2,3_DCA**	**U:Py2,3_DCA**		**Urea**	**Py2,5_DCA**	**U:Py2,5_DCA**	
1672	2437, 1865	2418, 1865	**Co-crystal**	3429, 3333	1696		**No co-crystal**
1587, 1455	1711	1716		2354			
	1687	1644		1708, 1672	1605	1707	
	1576	1298		1587			
1145	1258	109		1455	1451		
1038	1094			-	1241, 1173	1234	
Urea	**Py2,6_DCA**	**U:SbA**		**Urea**	**Py3,5_DCA**	**U:Py3,5_DCA**	
3429, 3333		2361, 1865	**Co-crystal**	3429, 3333		1721	**No co-crystal**
2354				2354			
1708, 1672	1697	1687		1708, 1672	1697, 1637	1669	
1587	1637, 1583	1646		1587	1583	1602	
1455		1455		-	1244	1152	
-	1244	1254					
Urea	**HipA**	**U:HipA**		**Urea**	**2,5DHBA**	**U:2,5DHBA**	
	1736	1744	**No co-crystal**	1670	1669	1669	**Co-crystal**
1672		1678		1587	1593	1520	
	1596	1596		1455	1453	1453	
1555	1552	1553			1219	1220	
1455	1489	1463					
1145	1175	1173					
Urea	**3,4DHBA**	**U:3,4DHBA**		**Urea**	**3,5DHBA**	**U:3,5DHBA**	
1587	1667	1678	**Co-crystal**	1672	1680, 1605	1680	**Co-crystal**
1455	1596	1594		1587, 1455	1479	1587	
	1289	190		1145	1158	1149	
	760	740		-			

Table S4. IR results of grinding experiments for co-crystallizations with nitro susbtituents.

Urea	Co-former	Ground mixture	Results	Urea	Co-former	Ground mixture	Results
Urea	**2NP**	**U:2NP**		**Urea**	**3NP**	**U:3NP**	
2354			**No co-crystal**		1672	1676	**Co-crystal**
1708, 1672		1671		1587	1594	1585	
1587	1583	1584		1455	1463	1477	
1455	1473	1473		1145, 976	1144	1148	
1145, 976	1131	1131		788, 699	811, 791	808, 772	
788, 699	868	866		788, 699	811, 791	808, 772	
Urea	**4NP**	**U:4NP**		**Urea**	**1,2DNB**	**U:1,2DNB**	
3429		3120	**Co-crystal**	1672	1526	1674, 1523	**Co-crystal**
1672	1457	1445		1587	1353	1585, 1350	
-	1328	1334		1455	790	1461, 787	
-	1110	1109					
	850, 816	844, 825					
Urea	**1,3DNB**	**U:1,3DNB**		**Urea**	**1,4DNB**	**U:1,4DNB**	
1672	1639, 1611	1596	**Co-crystal**	1672	1548	1602	**Co-crystal**
1587	1521	1504		1587	1526	1545	
1455	1424			1455	1341, 1105	1338	
	1326	1336					
Urea	**2NBA**	**U:2NBA**		Urea	**3NBA**	**U:3NBA**	
1587, 1670	1672	1685, 1608	**Co-crystal**		1504	1509	**Co-crystal**
1455	1587	1528		1455	1469	1459	
	1455	1484			1244	1242	
1133, 1290	1145	1257		788	792	789	
Urea	**4NBA**	**U:4NBA**					
1587	1684, 1599	1680, 1598	**Co-crystal**				
1455	1423	1419					
	1274	1275					
1133	1107	1106					

Table S5. IR results of grinding experiments for co-crystallization of amino acids**.**

Urea	Co-former	Grounded mixture	Results	Urea	Co-former	Grounded mixture	Results
Urea	**His**	**U: His**		**Urea**	**Arg**	**U: Arg**	
1672	1628	1676, 1620	**Co-crystal**	1587	1602	1607	**Co-crystal**
1587	1580	1597		1455	1471	1455	
1455	1453	1463			1344	1327	
	1340	1342		1133	1142	1145	
	1246	1244					
Urea	**Ala**	**U: Ala**		**Urea**	**Asp**	**U: Asp**	
1587	1586	1581	**No Co-crystal**		1504	1509	**No Co-crystal**
1455	1455	1458		1455	1469	1459	
	1235	1226			1244	1242	
	788	781		788	792	789	
	678, 659	680, 659					
Urea	**Glu**	**U: Glu**		Urea	Lys	**U: Lys**	
1708	-	1716	**Co-crystal**	1587		1681, 1623	**Co-crystal**
1455	-	1462			1574	1583	
-	1255	1256		1455		1450	
-	864	864		1133			

Table S6. IR results of grinding experiments for co-crystallization of N-oxides**.**

Urea	Co-former	Grounded mixture	Results	Urea	Co-former	Grounded mixture	Results
Urea	**Py_NO**	**U: Py_NO**		**Urea**	**TmPy**	**U: TmPy_NO**	
1672	1649	1615	**Co-crystal**	1587	1581	1618	**Co-crystal**
1587	1592	1597		1455	1472	1451	
1455	1467, 1430	1467			1382,1318	1382, 1310	
	1308	1385		1133	1136	1130	
1145	1211, 1002	1091			1010	1029	
	884	858		803		811	
Urea	**Py_NNO**	**U: Py_NNO**		**Urea**	**TmPy_NNO**	**U: TmPy_NNO**	
1587	1588	1662, 1598	**Co-crystal**		1523	1509	**Co-crystal**
1455	1481, 1440	1459		1455	1444, 1427	1459	
	1255	1298			1387, 1333	1242	
1145	1027	1108, 1090			1303		
	859	803		788	1113	789	
788	796	669			864		
Urea	**BiP_NO**	**U: BiP_NO**					
1708	1728	1857, 1666	**Co-crystal**				
1455	1585, 1530	1576, 1474					
-	1405						
-	1217	1237					
	1074, 988	1176, 1033					
	802, 732	844, 728					

Table S7. IR results of grinding experiments for co-crystallization of nicotinamides**.**

Urea	IN	U:IN		Urea	Me_N	U:Me_N	
	1660, 1619	1656, 1621	**Co-crystal**	1587	1585	1595	**Co-crystal**
	1550	1550		1555	1548	1558	
1455		1457		1455		1466	
	1407, 1389	1408, 1391		1038	1026	1021	
788		783					
Urea	**2Cl_N**	**U:2Cl_N**		**Urea**	**6Cl_N**	**U:6Cl_N**	
	1669, 1622	1662, 1624	**No co-crystal**		1650, 1611	1649, 1615	**No-cocrystal**
1587	1576	1585			1397	1402	
1455	-	1450		1145	1142	1142	
	1385	1383			1017	1018	
	1156	1158		803, 788	807, 783	805, 779	
	1070	1070					

Table S8. IR results of grinding experiments for co-crystallization of various**.**

Urea	Co-former	Grounded mixture	Results	Urea	Co-former	Grounded mixture	Results
Urea	**Biu**	**U: Biu**		**Urea**	**Ur**	**U:Ur**	
1672	1569	1695		1672	1650	1652	
1587		1587		1555	1574	1557	
1455	-	1457	**No co-crystal**	-	1345, 1297	1326	**No Co-crystal**
	1406, 1356	1412, --1356		-	1117	1115	
	1221	1218			987	987	
1145		1135					
	761, 708	762, 709					
Urea	**Ma**	**U: Ma**		**Urea**	**Glu**	**U: Glu**	
	1826	1828		1672		1682, 1630	
1672		1678		1587		1604	
1587, 1555		1616, 1595	**Co-crystal**	1455	1442, 1424	1459	**Co-crystal**
1455		1459			1332	1339	
	1373	1378				1021	
	1134	1140		1145		994	
Urea	**Im**	**U: Im**		**Urea**	**Re**	**U: Re**	
1672	1649	1647		1672	1604	1598	
1587				1587		1578	
1455	1505	1507, 1448	**Co-crystal**	1455	1486	1480	**Co-crystal**
	1268	1270			1166, 1143	1168, 1147	
Urea	**Lut**	**U: Lut**		**Urea**	**Phen**	**U: Phen**	
1672	1691	1683		1672	1644		
1587	1596	1627, 1605		1587	1502, 1420	1500	
1455	1447		**Co-crystal**	1455		1418	**Co-crystal**
	1383				1343	1342	
	1194				1090	1088	

1.6 Experimental details of solution crystallization

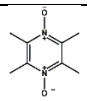
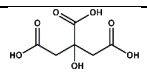
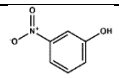
Table S9. Stoichiometric ratio, solvents used in the solution co-crystallization. The molecular weight of urea is 60g/mol (the mass of 0.10mmole of urea is 0.006gm, 0.05 is 0.003gm).

	Conformers	M.W. (g mol^{-1})	Mass (g)	mmole	Solvent	Ratio Co-former: urea
Aliphatic acids						
1	Citric acid (CA)	192	0.0192	0.10	Methanol, Water	1:2
2	Citramalic acid (CmA)	148.12	0.0148	0.10	Methanol, Ethanol	1:2
3	Malonic acid (MA)	52.00	0.0052	0.05	Methanol, Ethanol	1:2
4	Succinic acid (SA)	118.09	0.0059	0.05	Methanol, Ethanol	1:2
5	Fumaric acid (FA)	116.07	0.0058	0.05	Methanol, Ethanol	1:2
6	Glutaric acid (GA)	132.12	0.0066	0.05	Methanol, Ethanol	1:2
7	Adipic acid (AA)	146.14	0.0073	0.05	Methanol, Ethanol	1:2
8	Pimelic aid (PA)	160.17	0.0084	0.05	Methanol, Ethanol	1:2
9	Suberic acid (SbA)	174.20	0.0087	0.05	Methanol, Ethanol	1:2
10	Sebacic acid (SeA)	202.25	0.0101	0.05	Methanol, Ethanol	1:2
11	Tartaric acid (TA)	150	0.0150	0.10	Methanol, Ethanol	1:2
12	Maleic acid (MeA)	120	0.0120	0.10	Methanol, Ethanol	1:2
13	Azelaic acid (AzA)	188.22	0.0094	0.05	Methanol, Ethanol	1:2
Aromatic acids						
14	3-hydroxy benzoic acid (3HBA)	138.12	0.0138	0.10	Methanol, Ethanol	1:1
15	4-hydroxy benzoic acid (4HBA)	138.12	0.0138	0.10	Methanol, Ethanol	1:1
16	3-Amino benzoic acid (3ABA)	137.13	0.0137	0.10	Methanol, Ethanol	1:1
17	4-Amino benzoic acid (4ABA)	137.13	0.0137	0.10	Methanol, Ethanol	1:1
18	Phthalic acid (PtA)	166	0.0166	0.10	Methanol, Ethanol	1:2
19	Pyrazine-2-carboxylic acid (Py2_CA)	124	0.0124	0.10	Methanol, Ethanol	1:2
20	Pyrazine2,3-dicarboxylic acid (Py2,3_CA)	168	0.0168	0.10	Methanol, Ethanol	1:2
21	Pyridine2,5-dicarboxylic acid (Py2,5_CA)	168	0.0168	0.10	Methanol, Ethanol	1:2
22	Pyridine 2,6-dicarboxylic acid (Py2,6_CA)	168	0.0168	0.10	Methanol, Ethanol	1:2
23	Pyrazine3,5-dicarboxylic acid (Py3,5_CA)	168	0.0168	0.10	Methanol, Ethanol	1:2
24	Hippuric acid (HipA)	179	0.0179	0.10	Methanol, Ethanol	1:2
25	2,5-dihydroxybenzoic acid (2,5DHBA)	154	0.0154	0.10	Methanol, Ethanol	1:1
26	3,4-dihydroxybenzoic acid (3,4DHBA)	154	0.0154	0.10	Methanol, Ethanol	1:1
27	3,5-dihydroxybenzoic acid(3,5DHBA)	154	0.0154	0.10	Methanol, Ethanol	1:1
Nitro substituents						
28	o-nitrophenol (2NP)	140	0.028	0.20	DMF, Methanol	1:1
29	m-nitrophenol (3NP)	140	0.028	0.20	DMF, Methanol	1:1
30	p-nitrophenol (4NP)	140	0.028	0.20	DMF, Methanol	1:1
31	1,2-dinitrobenzene (1,2DNB)	168	0.0168	0.10	Methanol, Ethanol	1:2
32	1,3-dinitrobenzene (1,3DNB)	168	0.0168	0.10	Methanol, Ethanol	1:2
33	1,4-dinitrobenzene (1,4DNB)	168	0.0168	0.10	Methanol, Ethanol	1:2
34	o-nitrobenzoic acid (2NBA)	167	0.0167	0.10	Methanol, Ethanol	1:2
35	m-nitrobenzoic acid (3NBA)	167	0.0167	0.10	Methanol, Ethanol	1:2
36	p-nitrobenzoic acid (4NBA)	167	0.0167	0.10	Methanol, Ethanol	1:2

Amino acids						
37	Lysine (Lys)	146	0.0146	0.10	Methanol/Water (1:1)	1:1
38	Histidine (His)	155	0.0155	0.10	Methanol/Water (1:1)	1:1
39	Arginine (Arg)	170	0.017	0.10	Methanol/Water (1:1)	1:1
40	Aspartic acid (Asp)	133	0.0133	0.10	Methanol/Water (1:1)	1:1
41	Glutamic acid (Glu)	147	0.0147	0.10	Methanol/Water (1:1)	1:1
42	Alanine (Ala)	89	0.0089	0.10	Methanol/Water (1:1)	1:1
Nicotinamides						
43	Nicotinamide (N)	122	0.0122	0.10	Methanol, Ethanol	1:2
44	N-methyl-nicotinamide (Me_N)	136	0.0136	0.10	Methanol, Ethanol	1:2
45	2-chloro-nicotinamide (2Cl_N)	156	0.0156	0.10	Methanol, Ethanol	1:2
46	6-chloro-nicotinamide (6Cl_N)	156	0.0156	0.10	Methanol, Ethanol	1:2
N-Oxides						
47	Pyrazine N-oxide (Py_NO)	96	0.0096	0.10	Methanol, Ethanol	1:2
48	Tetramethyl pyrazine N-oxide (TmPy_NO)	110	0.011	0.10	Methanol, Ethanol	1:2
49	Pyrazine-NN-oxide (Py_NNO)	112	0.0112	0.10	Methanol, Ethanol	1:2
50	Tetramethylpyrazine-NNoxide (TmPy_NNO)	168	0.0168	0.10	Methanol, Ethanol	1:2
51	Bipyridine-N-oxide (BiP_NO)	172	0.0172	0.10	Methanol, Ethanol	1:2
Various						
52	Glucose (Gl)	180	0.018	0.10	Water	1:1
53	Biuret (Biu)	103	0.0103	0.10	Methanol, Ethanol	1:2
54	Imidazolidone (Im)	86	0.0086	0.10	Acetone	1:1
55	Maleimide (Ma)	97	0.0097	0.10	Methanol, Ethanol	1:2
56	Resorcinol (Re)	110	0.011	0.10	Acetone/Methanol (1:1)	1:1
57	2,6-Lutidine (Lut)	107	0.010	0.10	Water	1:2
58	Quinoline (Qui)	129	0.013	0.10	Methanol, Ethanol	1:1
59	Uric acid (Ur)	168	0.0168	0.10	Methanol, Ethanol	1:2
60	1,10-Phenanthroline (Phen)	180	0.0180	0.10	Methanol/Chloroform (1:2)	1:1

1.7 Experimental details of new co-crystals

Table S10. Experimental details for new co-crystals obtained in this study.

Co-crystals	**Co-former**	**Solvent**	**Experimental Stoichiometry (urea:co-former)**	**Crystal structure stoichiometry (urea:co-former)**	**M.P. (℃)**	**Morphology**
U:TmPy_NO		Ethanol	2:1	1:1	155-164℃	Plate, colorless
U:TmPy_NNO		Ethanol	2:1	1:1	205-208℃	Plate, colorless
U_2:CA		Ethanol, water	2:1	2:1	97-99℃	Prism, colorless
U:3NP		DMF, methanol	1:1	1:1	70-72℃	Plate, colorles

1.8 Crystal packing diagrams

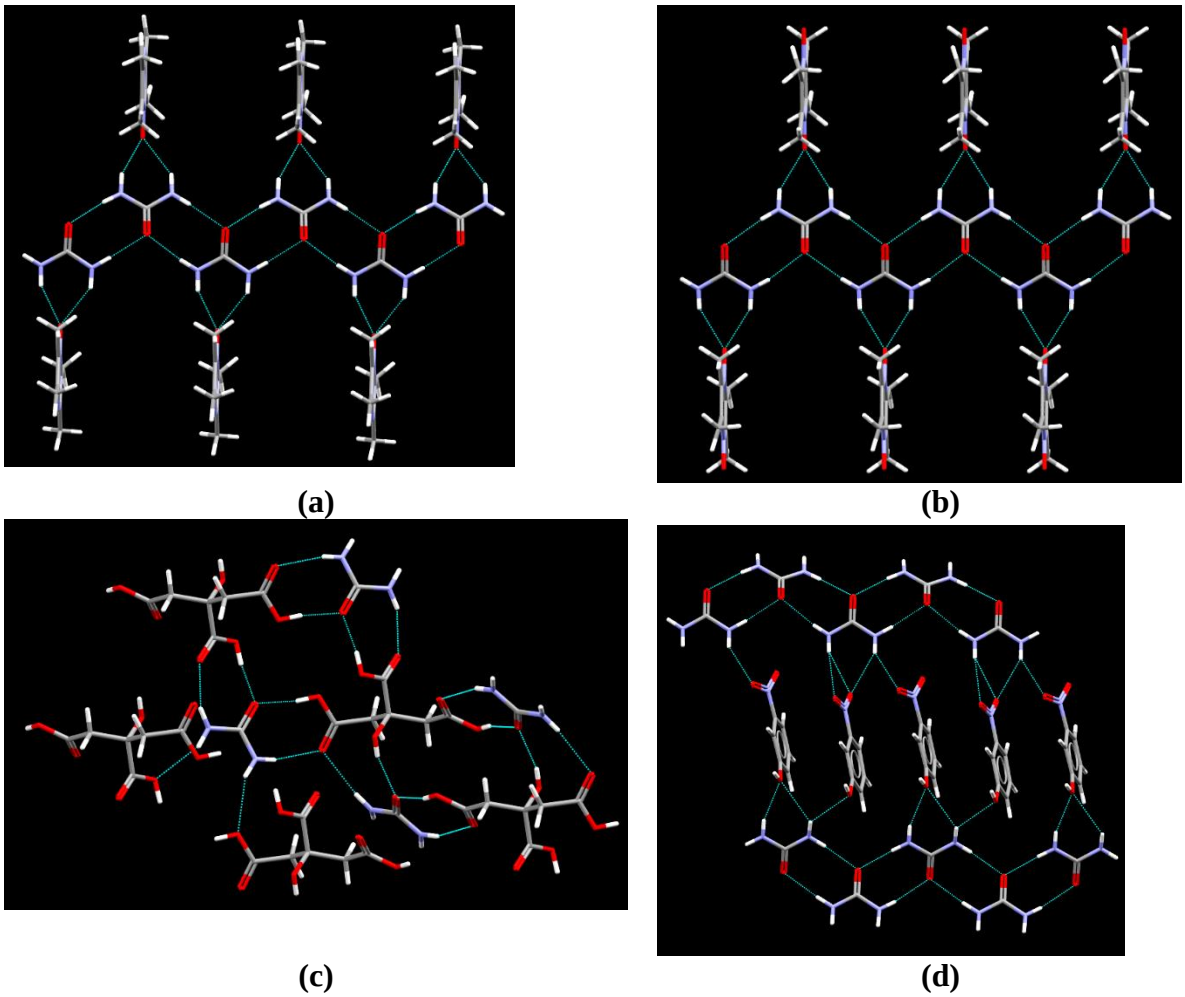


Figure S2. Crystal packing of **(a)** U:TmPy_NO, **(b)** U:TmPy_NNO, **(c)** U_2:CA and **(d)** U:3NP in the unit cell.

2. Solubility studies

2.1 Qualitative analysis

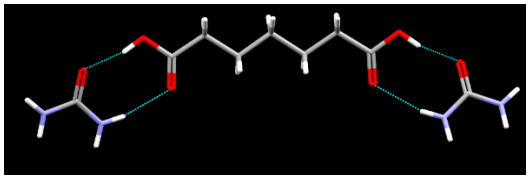
The qualitative analysis was performed as follows: Control experiment: 1 gm of pure urea was added to the vial and it was dissolved in approximately 1ml of water. Test experiment: An amount containing 1 gm of urea in each co-crystal was added into each vial and the water was added until the co-crystal was completely dissolved. The vials where more than 1 ml was needed to dissolve the solid were chosen as good candidates for initial solubility studies.

Figure S3. Qualitative analysis of urea and urea-co-former co-crystals in distilled water.

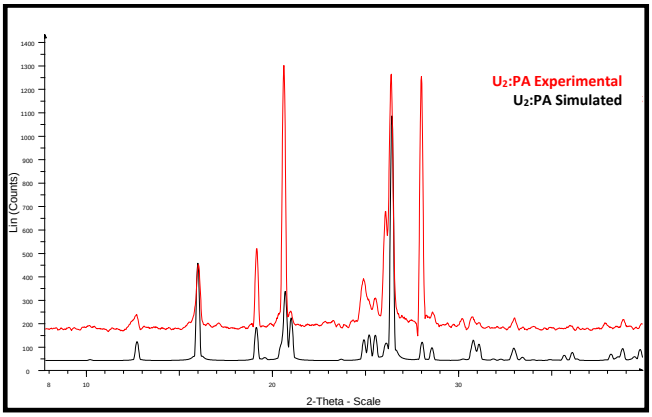
2.2 Large scale synthesis of co-crystals

2.2.1 Urea:pimelic acid (**U_2:PA**)

Urea (12.1g, 200 mmole) and PA (16.20 g, 100 mmole) were dissolved in 250 ml of ethanol solvent in 500ml round bottom flask. The mixture was refluxed at 40°C for 30 minutes. After 30 minutes, the resulting solution was cooled to 5° C using ice bath. The solid phase was harvested by vacuum filtration and dried at room temperature (22-23ºC) on a Fisherbrand filter paper for 12 hours to remove loosely bound solvent. (Melting point 118-121 °C).



(a) Refcode: EVETAB

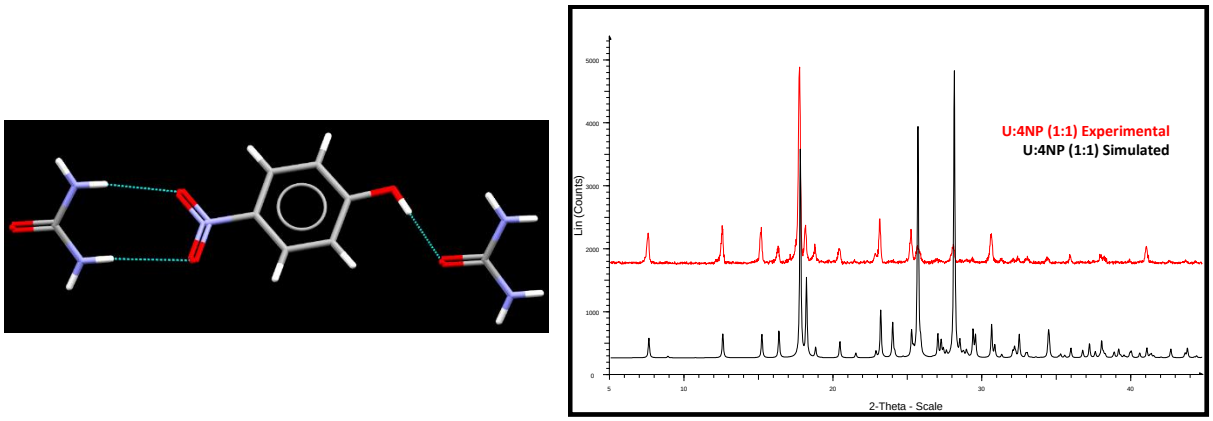


(b)

Figure S4. (a) crystal structure of **U_2:PA**[25], **(b)** Simulated and experimental XRD pattern comparison for **U_2:PA** co-crystal.

2.2.2 Urea:4Nitrophenol (**U:4NP**)

Urea (12.10g, 200 mmole) and 4NP(28.52 g, 200 mmole) were dissolved in 250 ml of methanol solvent in 500 ml round bottom flask. The mixture was refluxed at 40 °C for 45 minutes. After 45 minutes, the resulting solution was cooled to 5 °C using ice bath. The solid phase (yellow crystals) was harvested by vacuum filtration and dried at room temperature (22-23 °C) on a Fisherbrand filter paper for 12 hours to remove loosely bound solvent. (Melting point 98-100 °C).



(a) Refcode: GAVHUH **(b)**

Figure S5. (a) crystal structure of **U:4NP**[26], **(b)** Simulated and experimental XRD pattern comparison for **U:4NP** co-crystal.

2.3 Quantitative analysis

The solubility studies of pure urea, **U_2:PA**, and **U:4NP** cocrystals were done using gravimetric method. The equilibrium solubility of urea was determined by a gravimetric method.

Pure urea: A saturated solution of urea was prepared by dissolving known amount of urea in 10ml of distilled water in a 25ml beaker in trial 1. The beaker was sealed with para-film and stirred in a water bath to maintain constant room temperature (22-23°C) for 4 hours, 24 hours, 10 days and 1 month at room temperature. After stirring for given time, the remaining solid was filtered form the solution and dried overnight. The weight of the left over solid was recorded. The average concentration of the filtrate was determined by the mass difference of urea in 10ml of the water and left over solid after stirring. Three trials were performed at each 4 hours, 24 hours, 10 days and 1 month respectively. The same procedure was repeated for **U_2:PA** and **U:4NP** co-crystals.

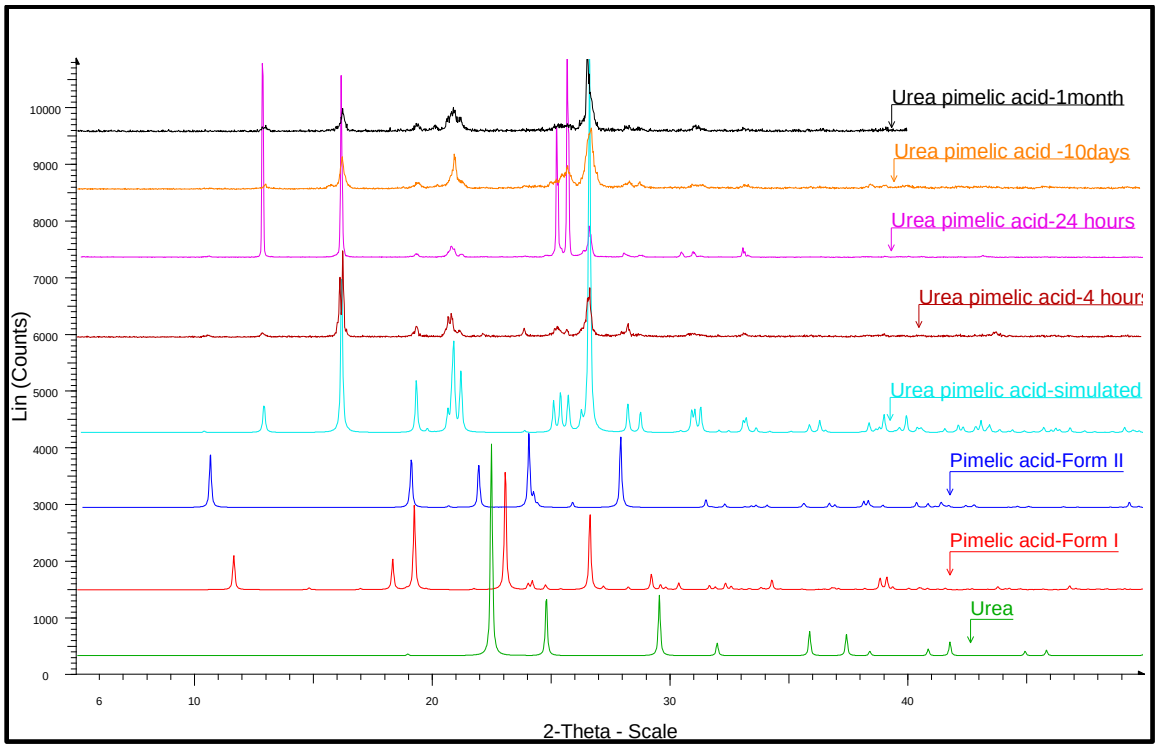


Figure S6. PXRD analysis of urea:pimelic acid (**U_2:PA**) after 4hours, 24 hours 10days and 1month.

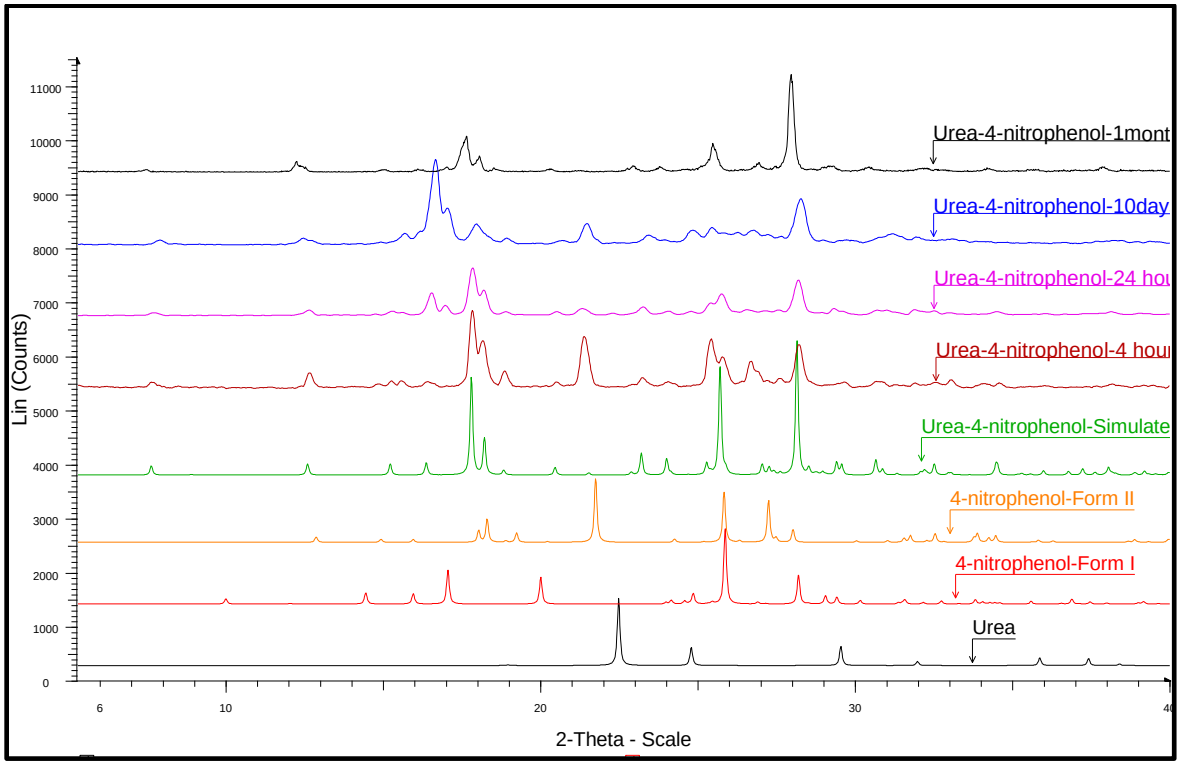


Figure S7. PXRD analysis of urea:4nitrophenol (**U:4NP)** after 4hours, 24 hours 10days and 1month.

Table S11. Solubility profile of pure urea, **U_2:PA** and **U:4NP** after 4 hours, 24 hours, 10days and 1 month.

	4 hours	**24 hours**	**10 days**	**1month**
Pure urea	17.79±0.02	17.25±0.20	17.22±0.24	17.18±0.3
Concentration of urea in **U_2:PA** co-crystal	0.84± 0.26	0.71±0.04	1.01±0.3	0.76±0.1
Concentration of urea in **U:4NP** co-crystal	0.28±0.04	0.2±0.09	0.30±0.03	0.27±0.07

5. Hygroscopicity studies

Hygroscopicity studies were performed at 43% (K_2CO_3) and 85% (KCl) humidity conditions using a humidity chamber. A supersaturated solution of K_2CO_3 and KCl was made in two different humidity chambers and was maintained saturated for a period of 1 month. Urea and two new solid forms (**U_2:PA** and **U:4NP**) were kept inside the humidity chamber and the samples were analyzed every week using qualitative and TGA and DSC analysis.

6. Powder X-ray diffraction (PXRD)

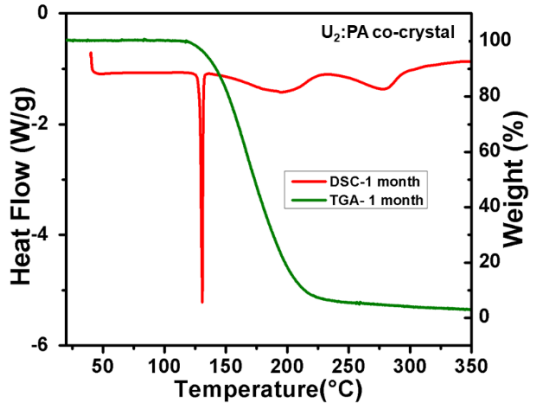
The PXRD spectra were collected on a bruker X-ray powder diffractometer using CuK (= 1.54059A)˚ radiation obtained at 30 kV and 15 mA. The scans were run from 5.0◦ to 30.0◦ 2, increasing at a step size of 0.05◦ 2 with a counting time of 2 s for each step.

7. Differential scanning calorimetry (DSC)

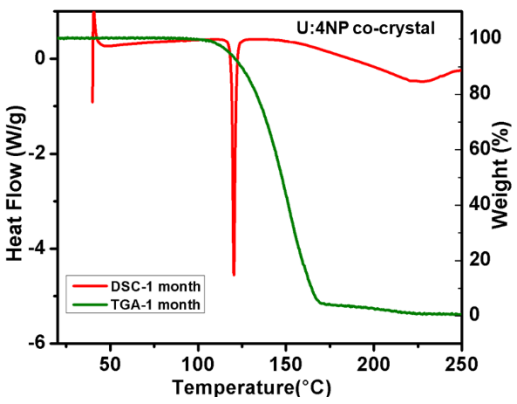
The melting points were measured with a Mettler Toledo DSC 822e differential scanning calorimeter (Greifensee, Switzerland). Accurately weighed samples (∼3 mg) were prepared in a covered aluminum crucible having pierced lids to allow escape of volatiles. The sensors and samples were under nitrogen purge during the experiments. The temperature calibration was carried out using the melting point of highly pure indium in the medium temperature range. Heating rate of 5 ◦C/min was selected.

8. Thermogravimetric analysis (TGA)

TGA was performed on a Mettler-Toledo TGA/SDTA 851e instrument. Approximately 2 mg sample was heated from 25 to 300 ◦C at 10 ◦C/min under nitrogen purge.



(a)



(b)

Figure S8. DSC-TGA profile of **(a) U_2:PA** and **(b) U:4NP** co-crystal after 1month exposure to 80% humidity conditions.

9. Crystallographic experimental details

All datasets were collected on a Bruker Kappa APEX II system using MoKα radiation. Data were collected using APEX2 software[27]. Initial cell constants were found by small widely separated "matrix" runs. Data collection strategies were determined using COSMO.[i] Scan speed and scan widths were chosen based on scattering power and peak rocking curves. Datasets were collected at -143 °C (**U:3NP**), and -153 °C (**U:TmPy_NO**; **U:TmPy_NNO**; **U_2:CA**) using an Oxford Cryostream low-temperature device. The unit cell constants and orientation matrix were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT,[28] 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.[29] The data were reduced with SHELXTL.[30] 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.

U: TmPy_NO – Coordinates of the urea protons H31A, H31B, H32A, and H32B were allowed to refine.

U:TmPy_NNO – This crystal sample was a non-merohedral twin and the data was processed with TWINABS.[31] The structure was solved using the processed data for Domain 1. Coordinates of the urea protons H31A, H31B, H33A, and H33B were allowed to refine.

U_2:CA – Coordinates of the carboxylic acid protons H11, H14, and H16; hydroxy proton H13; and the urea protons H21A, H21B, H22A, H22B, H31A, H31B, H32A, and H32B were allowed to refine.

U:3NP – This crystal sample was a non-merohedral twin and the data was processed with TWINABS.[31] The structure was solved using the processed data for Domain 1. Coordinates of the hydroxy protons H15 and H25; and the urea protons H1A, H1B, H3A, H3B, H5A, H5B, H7A, and H7B were allowed to refine.

Table S12. Hydrogen-bond geometry

Co-crystal	D-H...A/A°	D-H/ A°	H…A// A°	D…A// A°	D-H…O/ °
U:TmPy_NO	N31 H31A O11	0.87(2)	2.19(2)	2.941(3)	145.4(17)
	N32 H32A O11	0.87(2)	2.05(2)	2.841(3)	151.8(18)
	N31 H31B O31	0.87(2)	1.98(2)	2.844(3)	172.7(19)
	N32 H32B O31	0.87(2)	1.97(2)	2.845(3)	174(2)
U:TmPy_NNO	N31 H31A O11	0.833(17)	2.219(17)	2.9716(15)	150.3(13)
	N32 H32A O11	0.834(16)	2.189(16)	2.9496(15)	151.6(12)
	N31 H31B O32	0.849(16)	2.022(16)	2.8632(15)	170.3(15)
	N32 H32B O32	0.836(16)	2.054(16)	2.8880(15)	174.5(14)
U_2:CA	O11 H11 O21	0.84(2)	1.74(2)	2.5638(16)	166.7(19)

	O14 H14 O31	0.87(2)	1.71(2)	2.5803(15)	172.1(19)
	O13 H13 O21	0.820(19)	1.920(2)	2.7171(15)	163.8(19)
	O16 H16 O31	0.892(19)	1.71(2)	2.5997(15)	173.2(18)
	N21 H21A O12	0.88(2)	2.24(2)	3.0903(19)	162.6(18)
	N21 H21B O11	0.83(2)	2.33(2)	3.1508(18)	171.5(19)
	N22 H22A O15	0.86(2)	2.27(2)	3.1233(18)	169.7(18)
	N22 H22B O13	0.85(2)	2.22(2)	3.0342(18)	161.3(18)
	N31 H31A O15	0.78(2)	2.20(2)	2.9660(17)	166.4(19)
	N31 H31B O14	0.81(2)	2.41(2)	3.1647(18)	155.7(17)
	N32 H32A O17	0.88(2)	2.07(2)	2.9109(17)	159.9(18)
	N32 H32A O16	0.88(2)	3.14(2)	3.6618(19)	120.1(15)
U:3NP	N1 H1A O15	0.83(2)	2.57(2)	3.212(3)	134.9(19)
	N1 H1A O25	0.83(2)	2.42(2)	3.032(3)	131.2(19)
	N1 H1B O8	0.91(3)	2.07(3)	2.976(3)	174.(2)
	N3 H3A O15	0.82(3)	2.16(3)	2.950(3)	159.(2)
	N3 H3B O8	0.88(3)	2.05(3)	2.929(3)	174.(2)
	N5 H5A O28	0.82(3)	2.46(3)	3.253(3)	164.(2)
	N5 H5B O4	0.83(2)	2.13(3)	2.962(3)	172.(2)
	N7 H7A O18	0.81(3)	2.37(3)	3.079(3)	146.(2)
	N7 H7B O4	0.91(2)	2.09(3)	2.998(3)	175.(2)
	O15 H15 O4	0.90(3)	1.77(3)	2.666(2)	174.(3)
	O25 H25 O8	0.90(3)	1.82(3)	2.716(2)	175.(3)

Table S13. Crystallographic table for new co-crystals

Code	**U: TmPy_NO**	**U: TmPy_NNO**	**U_2:CA**	**U:3NP**
Formula moiety	$(C_8H_{12}N_2O)$ (CH_4N_2O)	(CH_4N_2O) $(C_8H_{12}N_2O_2)$	$(C_1H_4N_2O)_2$ $(C_6H_8O_7)$	$(C_6H_5NO_3)$ (CH_4N_2O)
Empirical formula	$C_9H_{16}N_4O_2$	$C_9H_{16}N_4O_3$	$C_8H_{16}N_4O_9$	$C_7H_9N_3O_4$
Molecular weight	212.26	228.26	312.25	199.17
Color, Habit	Plate, colorless	Plates, colorless	Prism, colorless	Plate, colorless
Crystal system	Orthorhombic	Monoclinic	Triclinic	monoclinic
Space group, *Z*	Pbca, 8	P2(1)/c, 16	P-1, 2	P2(1)/c, 8
***a*, Å**	12.646(13)	11.6812(10)	6.5395(5)	7.2016(19)
***b*, Å**	7.002(7)	13.2376(12)	6.7785(5)	26.812(6)
***c*, Å**	22.75(2)	6.9737(6)	15.2596(11)	9.497(2)
***α*, °**	90.00	90.00	81.525(2)	90
***β*, °**	90.00	100.298(4)	85.861(2)	104.392(13)
***γ*, °**	90.00	90.00	74.230(2)	90
Volume, Å^3	2014(3)	1060.98(16)	643.24(8)	1776.2(8)
Density, g/cm^3	1.400	1.429	1.612	1.490
***T*, °K**	120(2)	120 (2)	120 (2)	130.(2)
Crystal size, max x mid x min	0.42X0.20X0.08	0.42X0.36X0.10	0.42X0.42X0.36	0.52X0.38X0.06
X-ray wavelength, Å	0.71073	0.71073	0.71073	0.71073
***μ*, mm^{-1}**	0.102	0.109	0.146	0.124
Trans min / max	0.96/0.99	0.96, 0.98	0.941/0.95	0.99, 0.94

θ_{min}, °	6.33	1.77	1.35	2.69
θ_{max}, °	31.67	32.94	32.61	25.54
Reflections				
collected	9231	5593	19260	3273
independent	3171	5593	4243	3273
observed	2069	4089	3790	2360
R_{int}	0.0650	0.0345	0.0171	0.0532
Threshold expression	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$	$> 2\sigma(I)$
No. parameters	152	162	226	293
No. restraints	0	0	0	0
R_1 **(observed)**	0.0586	0.0529	0.0350	0.0517
wR_2 **(all)**	0.1694	0.1607	0.1013	0.1399
Goodness of fit (all)	1.055	1.078	1.057	1.052
ρ_{max}, ρ_{min}, e Å^{-3}	0.336, -0.251	0.335, -0.347	0.487, -0.297	0.310, -0.369
Completeness to 2θ limit	0.973	0.985	0.977	0.958

10. References:

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