CrystEngComm

Cite this: *CrystEngComm*, 2011, **13**, 4886

www.rsc.org/crystengcomm

PAPER

Propensity of formation of zipper architecture *vs.* Lincoln log arrangement in solvated molecular complexes of melamine with hydroxybenzoic acids†

Sunil SeethaLekshmi and T. N. Guru Row*

Received 7th February 2011, Accepted 4th May 2011
DOI: 10.1039/c1ce05179b

Molecular complexes of melamine with hydroxy and dihydroxybenzoic acids have been analyzed to assess the collective role of the hydroxyl (OH) and carboxyl (COOH) functionalities in the recognition process. In most cases, solvents of crystallization do play a major role in self-assembly and structure stabilization. Hydrated compounds generate linear chains of melamine molecules with acid molecules pendant resulting in a zipper architecture. However, anhydrous and solvated compounds generate tetrameric units consisting of melamine dimers together with acid molecules. These tetramers in turn interweave to form a Lincoln log arrangement in the crystal. The salt/co-crystal formation in these complexes cannot be predicted *apriori* on the basis of ΔpK_a values as there exists a salt-to-co-crystal continuum.

Introduction

Understanding molecular co-crystals and salts in terms of the spatial arrangement of intermolecular interactions is of utmost importance in supramolecular synthesis.[1] This knowledge is usually transformed to the design of robust synthons with much generality and predictability. Such an approach is usually found in the development of molecular complexes, for example novel pharmaceutical formulations with better stability, solubility and bioavailability.[2] Some of the best studied interactions in crystal engineering are the homomeric and heteromeric synthons of carboxylic acids and carboxamides.[3] Studies pertaining to the acid-triazine heterosynthons are limited compared to the copious acid-pyridine heterosynthons.[3e] This has prompted us to study the interactions present in a series of complexes with acids and a triazine.

The triazine compound melamine (2,4,6-triamino-1,3,5-triazine, **ML**) is interesting in a crystal engineering perspective due to its symmetry and the availability of several hydrogen bond donor and acceptor functionalities. In the solid state, **ML** forms complementary arrays of N–H···N hydrogen bonds resulting in a 2D network (Scheme 1A). It has been demonstrated that depending on the extent of protonation of the triazine ring, the dimensionality of the hydrogen bonded network decreases from 2D to 1D and eventually to 0D (Scheme 1B and C).[4]

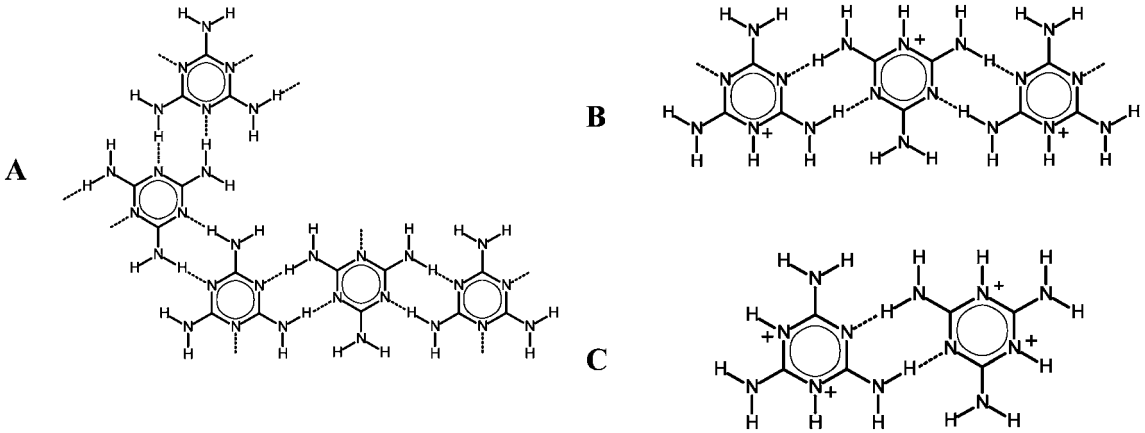
One of the most intriguing and well-known assemblies involving **ML** is the *rosette* architecture formed with cyanuric acid.[5] In recent times, **ML** formed the central stage, when several companies in China were implicated in a scandal involving infant feed formulation which was adulterated with melamine, resulting in renal failure among children.[6] Lu and co-workers developed sensors based on the recognition patterns existing between melamine and cyanuric acid to establish the presence of melamine in milk products.[7] This clearly emphasizes the importance of an understanding of the recognition process involving melamine. With carboxylic acids, **ML** generally forms hydrated salts as revealed from a CSD analysis.[8] It was noted that in the molecular complexes of **ML** with gallic acid, tartaric acid and citric acid, carboxyl and hydroxyl groups participate in extensive hydrogen bonding.[9] However, the collective influence of hydroxyl and carboxyl groups in the recognition with **ML** have not been systematically evaluated. In this context, we have prepared and analyzed molecular complexes of **ML** with hydroxybenzoic acids and isomers of dihydroxybenzoic acids (Scheme 2). We report and discuss these molecular complexes in terms of synthon formation, structural variations due to hydration or solvation and salt-to-co-crystal continuum.

Experimental

All compounds were purchased from Sigma-Aldrich and were used without further purification. Co-crystallization experiments were carried out by dissolving equimolar compounds from a 1 : 1 CH_3CN–H_2O solution followed by slow evaporation at room temperature. In **6**, the co-crystallization experiments were carried out from a 1 : 1 CH_3CN–DMF (*N*,*N*-dimethylformamide) solution. Single crystals suitable for X-ray diffraction studies were obtained over a period of one week. Co-crystallization of 3-hydroxybenzoic acid with **ML** did not yield crystals suitable for

Solid State & Structural Chemistry unit, Indian Institute of Science, Bangalore, 560 012, India. E-mail: ssctng@sscu.iisc.ernet.in; Fax: +91 80 2360 1310; Tel: +91 80 2293 2796

† Electronic supplementary information (ESI) available. CCDC reference numbers 782608–782613. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ce05179b



Scheme 1 Hydrogen bond patterns exhibited by the **ML** molecule (A) 2D, (B) 1D and (C) 0D depending on the extent of protonation.

single crystal X-ray diffraction studies, even after repeated attempts from several solvents.

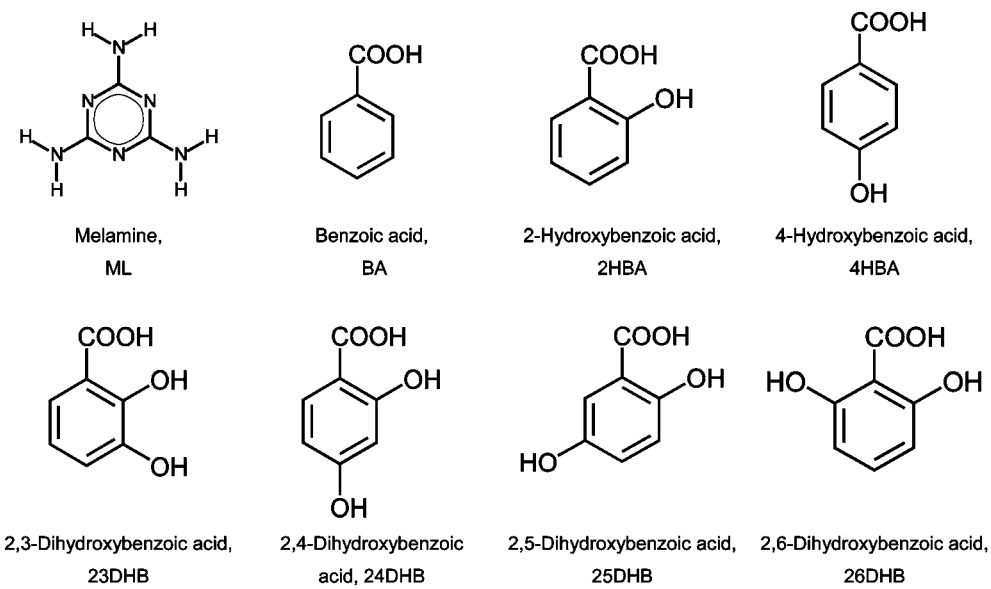
Crystallography

Single crystals of the complexes **2–7** were chosen using an Olympus microscope supported by a rotatable polarizing stage. Single crystal data for the complexes **2–7** were collected on an Oxford single crystal X-ray diffractometer (Microsource: Mova; Detector: Eos) with a four-circle κ goniometer employing a graphite-monochromatized Mo–Kα ($\lambda_{\text{Mo-K}\alpha}$ = 0.71073 Å) radiation. The measured intensities were corrected for Lorentz and polarization effects. The data were reduced using CrysAlisRED (special programs available with the diffractometer) and an analytical absorption correction (after Clark and Reid) was applied.[10] Structure solution and refinements were performed by the SHELX97 using the WinGX suite.[11] Table 1 lists all the relevant crystallographic information. The non-hydrogen atoms were refined anisotropically and hydrogen atoms bonded to C, N and O atoms were positioned geometrically and refined using a riding model. Hydrogen atoms with water of crystallization were located from a difference Fourier synthesis and were refined isotropically. In **6**, the water molecules and the disordered DMF molecules were refined isotropically. The ORTEP diagrams of the complexes are provided in the ESI.† For **2–7**, characteristic data of hydrogen bonds (bond lengths in Å, angles in °) are given in Table 2.

X-ray powder diffraction (PXRD) data were collected on a Philips X'pert Pro X-ray powder diffractometer (Cu–Kα radiation) equipped with an X'cellerator detector. The scan range, step size, and time per step were 2θ = 5.00–40°, 0.02°, and 25 s, respectively. The combined PXRD plot of the complexes is given in the ESI.†

Thermal analysis

Thermogravimetric analyses were carried out using a Mettler Toledo TG/DSC-1 thermogravimetric analyzer and the



Scheme 2 Molecular structures of the hydroxyl acids studied with melamine.

Table 1 Crystallographic information of **2–7**

	2	**3**	**4**	**5**	**6**	**7**
Formula	$2(C_3H_7N_6)$,$2(C_7H_5O_3)$, (C_2H_3N)	$(C_3H_7N_6)$, $(C_7H_5O_3)$, $2(H_2O)$	$3(C_3H_7N_6)$, $3(C_7H_5O_4)$, $11(H_2O)$	$(C_3H_7N_6)$, $(C_7H_5O_4)$, $2(H_2O)$	$2(C_3H_6N_6)$, $2(C_7H_6O_4)$, $2(C_3H_7NO)$, $2(H_2O)$	$(C_3H_7N_6)$, $(C_7H_5O_4)$
CCDC no.	782612	782613	782608	782609	782610	782611
Formula wt	569.57	300.29	1016.77	316.29	730.64	280.26
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$C2/c$	$P2_1/c$
a (Å)	16.691(8)	7.571(1)	10.811(1)	15.788(1)	38.011(5)	14.372(1)
b (Å)	8.577(4)	10.857(1)	12.298(1)	12.160(1)	9.212(5)	8.549(1)
c (Å)	20.692(8)	16.477(1)	19.580(1)	7.161	20.430(5)	20.671(2)
α (°)	90	87.12(5)	82.23(4)	90	90	90
β (°)	117.83(3)	85.51(5)	79.12(5)	96.56(5)	99.44(5)	114.23(1)
γ (°)	90	82.63(5)	64.53(5)	90	90	90
V (Å^3)	2620(2)	1337.96(15)	2303.7(3)	1365.78(14)	7057(4)	2316(4)
Z	4	4	2	4	8	8
Dcalc (g cm^{-3})	1.444	1.491	1.466	1.538	1.375	1.607
T (K)	298(2)	298(2)	150(2)	298(2)	298(2)	150(2)
μ (mm^{-1})	0.110	0.121	0.127	0.128	0.111	0.128
2θ range (deg)	50.00	50.46	50.48	50.20	50.48	50.48
total reflns	5980	25272	43060	13382	34754	21344
unique reflns	4203	4818	8323	2437	6376	4184
reflns used	1247	2815	4456	1363	3172	1676
no. of parameters	371	379	640	223	469	361
GOF on F^2	0.689	0.944	1.112	0.900	0.972	0.771
Final $R1$, $wR2$	0.0712, 0.1620	0.0459, 0.1032	0.0797, 0.2058	0.0659, 0.1608	0.0784, 0.2389	0.0464, 0.0838

experiments were carried with a heating rate of 5 °C min^{-1} from 35–350 °C, under a nitrogen atmosphere. The TG plots are given in the ESI.†

Results and discussion

Benzoic acid–ML complex, 1

Benzoic acid (**BA**) forms salts with **ML**, incorporating two molecules of water. Two polymorphic structures of the complex are reported, one crystallizing in a monoclinic space group ($C2/c$, $Z = 8$)[12] and the other in an orthorhombic space group ($Pbca$, $Z = 8$).[13] In both cases, **ML** forms one-dimensional tapes through centrosymmetric N–H···N hydrogen bonds. The benzoate molecules arrange as pendants to the **ML** tapes through N–H···O$^-$ and N$^+$–H···O$^-$ ($R^2_2(8)$) interactions, as shown in Fig. 1. The lattice water molecules hold the adjacent tapes together through N–H···O, O–H···O and O–H···O$^-$ hydrogen bonds and the two polymorphic structures show significant differences in the crystal packing (see ESI†). The packing features of the **BA–ML** complexes will be employed as a reference in subsequent discussions to evaluate the synergic effect of both hydroxyl and carboxyl groups in hydrogen bond formation with melamine.

2-Hydroxybenzoic acid–ML complex, 2

The asymmetric unit of **2** consists of two molecules each of **2HBA** and **ML** along with a molecule of acetonitrile (Space group $P2_1/c$; $Z = 4$). The **ML** is mono-protonated and forms dimers through centrosymmetric N–H···N ($R^2_2(8)$) hydrogen bonds. The **2HBA** units cap the **ML** dimers resulting in a tetramer (Fig. 2). In **2HBA** the hydroxyl group is locked in an intramolecular interaction with the carboxylate and hence is devoid of any structure stabilization role. Acetonitrile molecules interact with these tetramers through N–H···N hydrogen bonds. Two adjacent tetramer units form N–H···O$^-$ interactions and they interweave to form a Lincoln log arrangement in three-dimensions.

4-Hydroxybenzoic acid–ML complex, 3

4-Hydroxybenzoic acid (**4HBA**) with **ML** crystallizes as a hydrated salt (Triclinic, $P\bar{1}$) and the asymmetric unit consists of two molecules each of **4HBA** and **ML** along with four water molecules. The **ML** units form one-dimensional tapes and the benzoate units pendant to this, as observed in **1**. Such units are further connected with each other through several hydrogen bonds (O–H···O$^-$, O–H···O and N–H···O), involving the OH group and lattice water molecules, to generate a zipper architecture in two-dimensions (Fig. 3).

2,3-Diydroxybenzoic acid–ML complex, 4

Upon co-crystallizing from an acetonitrile–water (1 : 1) mixture, 2,3-dihydroxybenzoic acid (**23DHB**) and **ML** yield a 1 : 1 molecular complex, **4**. Three molecules each of **23DHB** and **ML** together with eleven water molecules constitute the asymmetric unit. The acid units are deprotonated and form a salt with **ML**. It is interesting to note that among the three symmetry independent **23DHB** molecules, two have their hydroxyl groups in a *syn-anti* conformation and the third has a *syn-syn* orientation. The *ortho*-hydroxyl groups of the acids exhibit a similar orientation as in **2** and have intramolecular interactions with the carboxylate moiety.

In the crystal, **ML** molecules form one-dimensional tapes and the **23DHB** units pendent to the tapes. The molecular tapes constitute symmetry independent benzoate units with **23DHB** in the *syn-syn* and *syn-anti* (green and yellow respectively in Fig. 4a)

Table 2 Characteristic data of hydrogen bonds [bond lengths in Å, angles in °][a]

	N–H···N	N–H ···O	N–H ···O$^-$	N$^+$–H ···O$^-$	O–H ···O	O–H ···O$^-$	O–H···N	C–H···O	C–H···N
2	1.93 2.93 170	2.02 2.88 141	1.82 2.82 172	1.72 2.72 168		1.67 2.53 143			2.52 3.50 151
	2.04 3.01 161	2.00 2.99 168	1.89 2.79 146	1.84 2.79 154		1.56 2.44 146			2.85 3.76 142
	2.16 3.17 175		1.94 2.90 156						
	2.28 3.02 130		2.14 3.00 142						
3	1.97 2.98 173	2.00 2.99 166	1.88 2.85 161	1.62 2.63 173	1.70 2.66 166	1.80 2.77 168		2.92 3.82 140	
	2.04 3.04 175	2.08 3.08 165	1.89 2.87 162	1.63 2.63 170	1.75 2.67 155	1.82 2.79 166			
	2.06 3.06 176	2.15 2.95 135			1.90 2.83 157	1.87 2.85 170			
		2.17 3.10 154			1.92 2.85 158	1.91 2.83 155			
						1.92 2.84 155			
4	1.93 2.93 169	1.91 2.89 162	1.89 2.86 161	1.61 2.61 168	1.80 2.78 174	1.63 2.49 144		2.67 3.72 163	
	1.95 2.95 170	1.93 2.91 164	1.91 2.85 155	1.66 2.67 173	1.94 2.84 150	1.71 2.56 143		2.86 3.76 140	
	1.95 2.96 177	2.00 2.95 156	1.93 2.92 169	1.79 2.77 165		1.73 2.59 144		2.93 3.94 154	
	1.97 2.98 177	2.02 3.00 163							
	2.02 3.02 171	2.08 2.97 146							
	2.03 3.04 179	2.09 2.87 132							
		2.10 2.87 131							
		2.12 2.99 144							
5	2.04 3.01 160	1.95 2.94 168	1.85 2.85 172	1.65 2.66 174	1.76 2.71 158	1.70 2.56 143		2.44 3.43 151	
	2.06 3.05 164	2.17 3.09 150			1.93 2.83 151	1.86 2.82 164			
					2.09 2.98 151	1.91 2.76 143			
6	2.00 3.01 176	1.95 2.94 167	1.88 2.88 171		1.63 2.60 169		1.70 2.69 177	2.32 3.18 135	2.64 3.56 143
	2.01 3.02 174	1.96 2.94 164	1.89 2.87 163		1.65 2.50 143		1.71 2.68 167	2.57 3.59 156	2.93 3.99 169
	2.36 3.04 124	2.01 2.99 163	2.31 3.13 137		1.68 2.53 142			2.78 3.58 130	
		2.10 3.09 167			1.79 2.77 175			2.78 3.77 152	
		2.22 3.02 135							
7	1.98 2.98 173	1.96 2.93 160	1.85 2.81 159			1.61 2.49 146			
	2.08 3.09 176	1.96 2.96 170	1.86 2.82 155			1.66 2.54 146			
		2.10 2.91 136	1.93 2.88 157			1.68 2.55 145			
		2.11 2.92 134	2.08 3.02 155						
		2.13 2.89 130	2.11 3.00 146						
			2.24 3.09 141						
			2.27 3.12 140						

[a] The three columns correspond to H···A, D···A (Å) distances and D–H···A (°) angle [A= acceptor, D = donor].

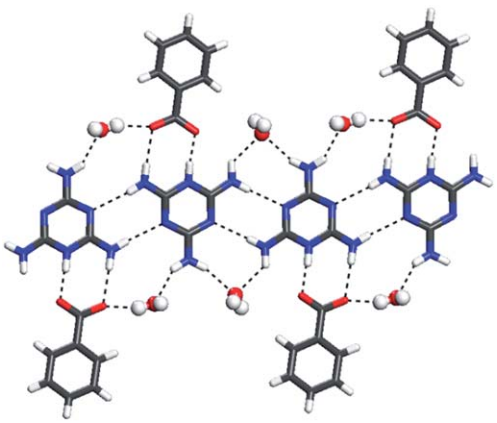


Fig. 1 A typical arrangement of molecules in **1**.

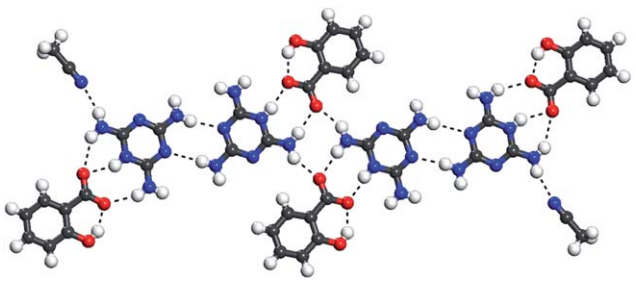


Fig. 2 The hydrogen bonding pattern observed in **2**.

conformations make distinct tapes which are arranged in an XYY XYY sequence in two-dimensions. Water molecules occupy the cavity generated by the inefficient crystal packing and form a unique one-dimensional undecameric water cluster with an average O···O distance of 2.846 Å (Fig. 4b).[14]

2,4-Diydroxybenzoic acid–ML complex, 5

The crystal packing in **24DHB** with **ML** is quite similar to **3**. This is not surprising as the *ortho*-hydroxyl group is involved in an intramolecular interaction with the carboxylate and is not involved in any structure directing role. The 4–OH moiety together with the lattice water (through O–H···O and N–H···O hydrogen bonds) stabilizes the zipper structure (Fig. 5).

2,5-Diydroxybenzoic acid–ML complex, 6

Two molecules each of **25DHB**, **ML**, water and DMF (which are disordered) constitute the asymmetric unit of **6**. Of the two symmetry independent **25DHB** molecules, the OH groups of one is in the *syn-syn* and other is in the *syn-anti* conformation. The **ML** units make dimers through N–H···N hydrogen bonds and their further extension to a one-dimensional tape is restricted by the interaction of **25DHB** units (Fig. 6a). This in fact is similar to

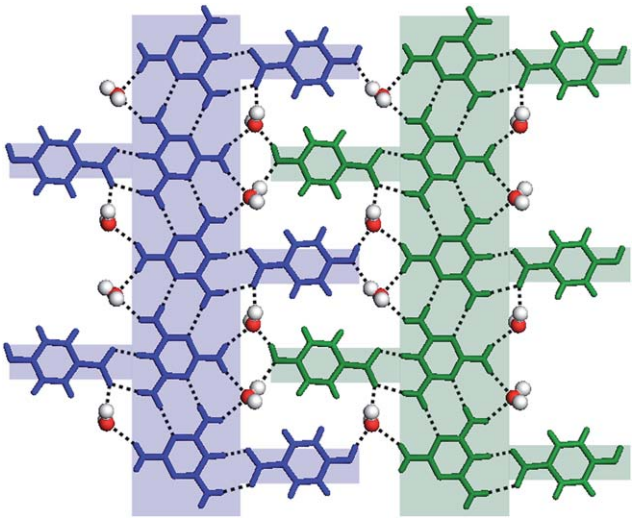


Fig. 3 Zipper architecture observed in **3**. **ML** tapes and the acid pendants are shown in two different colours.

the case observed in **2**. However, unlike in **2**, one of the **25DHB** units retains its COOH functionality while the other undergoes a proton transfer towards the **ML** unit (C–O distance is 1.22, 1.30 Å; 1.25, 1.26 Å, respectively, for the protonated and deprotonated acid units).

The *ortho* hydroxyl group is locked in an intramolecular interaction. However, the OH functionality in the 5-position, exhibiting two distinct conformations, makes O–H···O hydrogen bonds with DMF molecules as shown in Fig. 6a. The acid–**ML** tetramer units stack in a Lincoln log arrangement in three-dimensions (Fig. 6b). Though there exists water molecules in the

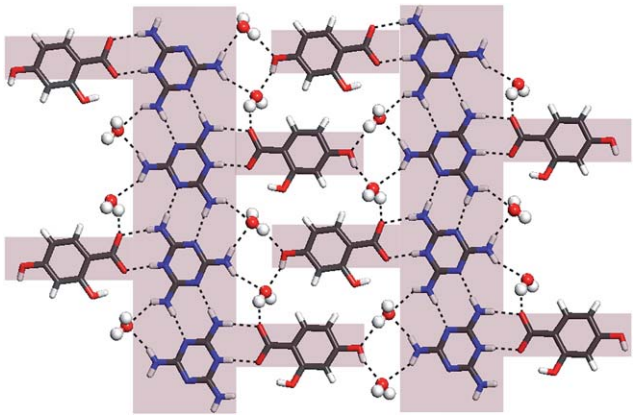


Fig. 5 The zipper assembly obtained in **5**.

crystal lattice, it has no structure directing role, as in the previous hydrated structures **1**, **3**, **4** and **5**, rather it stabilizes the assembly together with the DMF molecules.

2,6-Diydroxybenzoic acid–ML complex, 7

26 DHB yielded a salt with **ML**. Tetramer units consisting of **ML** dimers and the **26DHB** molecules as capping agents constitute the basic recognition unit. It is interesting to note that even in the absence of any solvent molecules, **7** gives a recognition pattern similar to the one observed in **2** and **6** and forms a Lincoln log network (Fig. 7). Several attempts to obtain the hydrated/solvated complex with a variety of solvent combinations were unsuccessful. This can be attributed to the absence of any hydrogen bonding functionality at the rear of the tetramer units. Both the hydroxyl groups are locked in an intramolecular

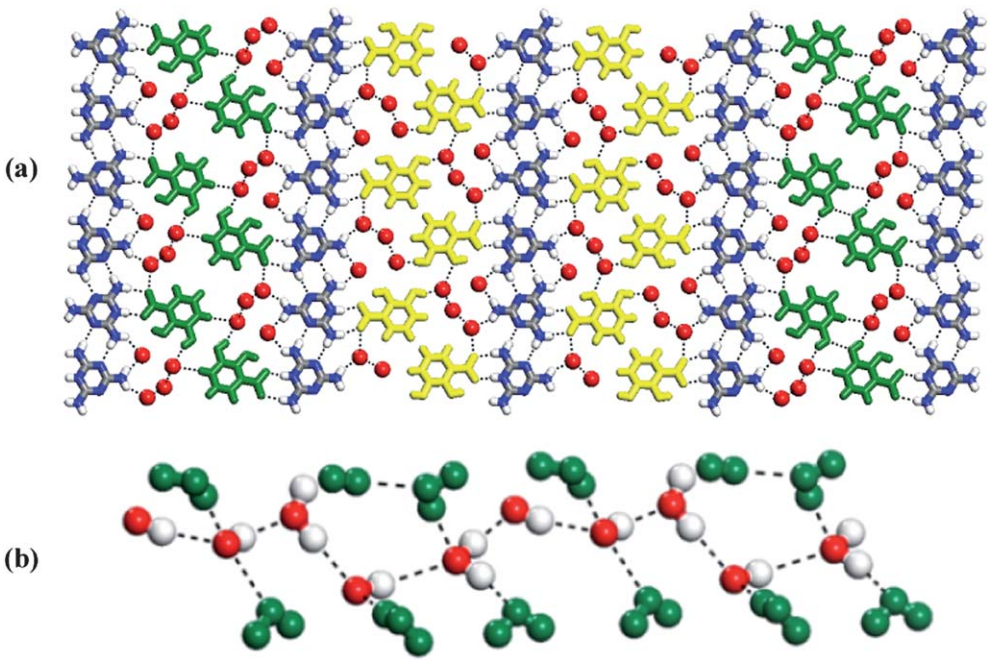


Fig. 4 The recognition patterns existing between the acid and **ML** molecules in **4**. (a) The symmetrically distinct molecular tapes formed by the acid molecules with *syn-syn* (green) and *syn-anti* (yellow) conformations. The water molecules present in the cavity is given in red colour. (b) The undecamer water cluster. The pendent water molecules to the one-dimensional water chain are represented in green.

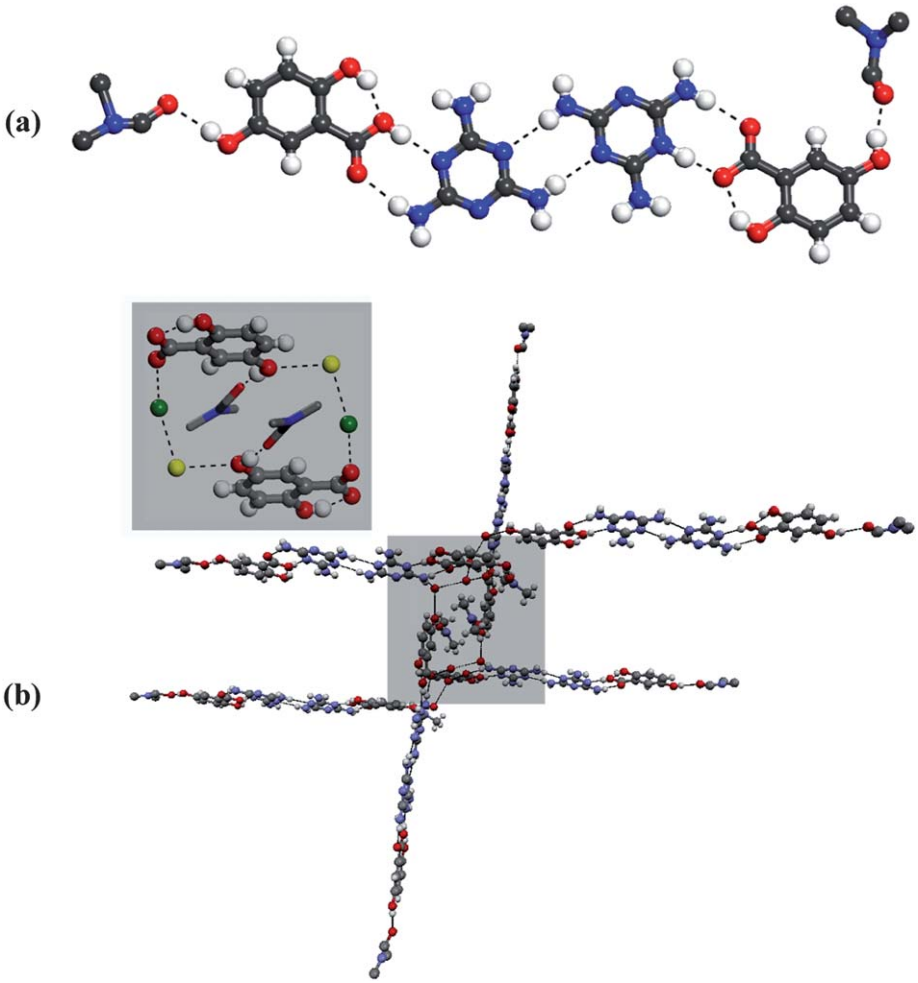


Fig. 6 (a) The basic hydrogen bonding pattern present in **6**. The disorder associated with the DMF molecules is not shown for clarity (b) The Lincoln log arrangement. Inset showing the solvents of crystallization DMF and water stabilizing Lincoln log arrangement.

interaction with the carboxylate and are not available to interact with any incoming molecular species.

Analysis of the hydrated/solvated structures

Hydrates are multiple-component systems that contain included water molecules in the crystal lattice. Although there is no definite rule for the prediction of hydrate formation, it is widely accepted that water molecules are incorporated into the crystal lattice when there is an imbalance in the number of donor–acceptor functionalities.[15] Infantes *et al.* reported that the probability of organic compounds forming hydrated structures increases with an increasing number of polar chemical groups in the molecule.[16] They also noted that molecules possessing groups like >C═O, COOH, $CONH_2$, NH, NH_2 and OH have a greater tendency to form hydrated structures. In the analysis of the structural features of the complexes of **ML** presented in the previous sections, these postulates have been found to be validated, particularly in terms of the number of polar functionalities in the crystal lattice. A CSD analysis further suggests that the molecular complexes of **ML** with acids have a greater tendency to form hydrated structures.[8] In the majority of these complexes the COOH group is deprotonated, resulting in increased instances of hydration. This is in agreement with the fact that compared to carboxylic acid, the hydration affinity of carboxylate is high. From a CSD analysis it is evident that 2671 out of 7722 hits for carboxylate (35%) are hydrated. However, it is only

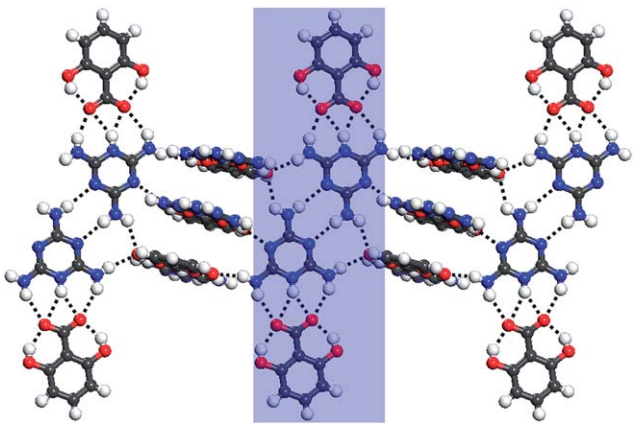


Fig. 7 The Lincoln log network present in **7**. A representative tetramer unit is highlighted.

2332 out of 13128 for carboxylic acid (18%). The values are comparable with those reported by Infantes *et al.*[16]

In the hydrated complexes (**1**, **3–6**), TG analysis reveals that the onset of the loss of lattice water molecules is below 100 °C (Table 3). This, in fact, suggests that the water molecules are loosely bound and belong to the Class-1 type of hydrates reported by Zaworotko and co-workers.[17] Since water of hydration plays a pivotal role in the structure stabilization, they can be categorized in the 'water as integral part', according to the classification of water of crystallization by Varughese *et al.*[18] The hydrated complexes **3**, **4** and **5** show a similar recognition pattern and form a zipper architecture (Scheme 3A). This is clearly distinct from the acid–**ML** tetramer units and the Lincoln log arrangement observed in the solvated/non-solvated complexes **2**, **6** and **7** (Scheme 3B). Although the **ML**–benzoic acid complex **1** has similar hydrogen bonding pattern with the benzoic acid forming pendants as those in **3**, **4** and **5**, formation of a zipper architecture is not observed. This can be attributed to the absence of a hydrogen bonding functionality on the benzoic acid moiety to extend hydrogen bonding features which are essential in the zipper architecture. In the complexes of hydroxy acids with 3- and 4-hydroxyl functionalities, an extended network with water results in a zipper architecture. Thus, it is evident that a hydroxyl functionality on the pendent acid together with water is playing a co-operative role and is a requisite element in the transformation of the one-dimensional melamine chains to zipper architectures in the **ML–HBA** complexes. It is noteworthy that the structure of **7** adopts a Lincoln log network as it is not solvated and lacks any functionalities at the opposite end of the carboxylate moiety.

The extent of hydration in **4**, wherein the cavity formed by the inefficient packing of the molecules is occupied by a one-dimensional undecameric water cluster with a unique topology, is of interest. The formation of one-dimensional water clusters with this particular topology is apparently imposed by the shape of the host channels. Water clusters play a vital role in the stabilization of supramolecular systems both in solution and in the solid state and one-dimensional water chains represent a unique form of water.[19] Many of the biological processes appear to depend on the properties of water clusters.[20] Usually these water clusters are stabilized by strong hydrogen bonds formed between neighboring water molecules as well as the one between water molecules and donor/acceptor groups associated with channels. Several experiments are currently underway which include careful DSC/TG analysis of the loss of water molecules and variable temperature XRD to systematically evaluate the impact of dehydration in these structures.

Conformational analysis

It is noteworthy that in **4** and **6** the **DHBA** molecules exhibit two different conformations. In **4**, two out of the three symmetry independent **23DHB** molecules exhibit a *syn–anti* conformation while the remaining one make a *syn–syn* orientation (Fig. 8a). It is quite interesting to note that two energetically distinct conformers co-exist in the crystal lattice. It is noteworthy that in the co-crystal/salt literature of hydroxybenzoic acids, there exists only one example, in the case of **26DHB**, wherein both the *syn–syn* and *syn–anti* conformers co-exist (Data from the CSD analysis is given in Table S1, ESI†). Similarly in **6**, the **25DHB** molecules exhibit different conformations (*syn–syn* and *syn–anti*) as given in Fig. 8b. The occurrence of different orientations shows the conformational flexibility of the OH groups and its reliability towards various molecular recognition phenomena. Although the *ortho*- hydroxyl groups in these acids are locked in intramolecular hydrogen bonds, there exist no such restrictions for the *meta* –OH groups. It may be interpreted that the co-existence of the energetically different conformationally flexible molecules observed in **4** and **6** occur preferentially to augment the formation of hydrogen bonds, leading to robust frameworks in the lattice.

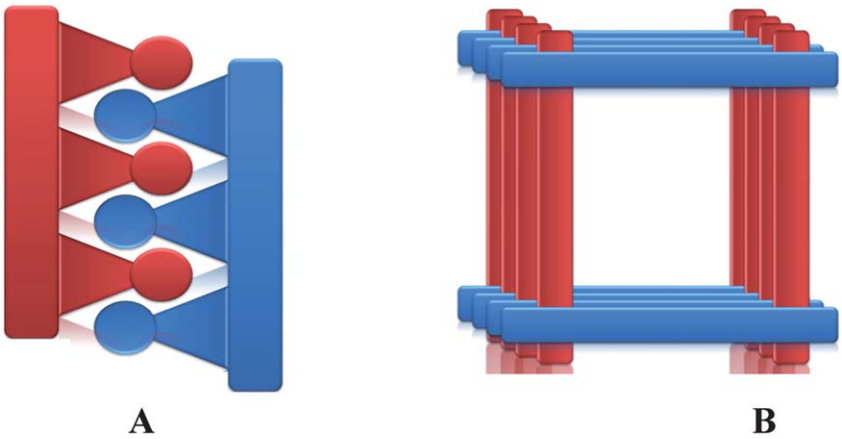
Salt–to-co-crystal continuum

The pK_a difference between the constituents is usually regarded as a decisive factor in the formation of co-crystal or salt.[21] A well-accepted rule of thumb in predicting the salt formation is that a proton transfer from acid to base can be anticipated if the ΔpK_a (ΔpK_a = pK_a of base − pK_a of acid) is greater than 3.[22] A negative ΔpKa would yield a co-crystal. However in the case of melamine, such a prediction is void as a CSD analysis indicates that the salt-to-co-crystal ratio is very high for the complexes of **ML** with carboxylic acids wherein the components recognize each other through N^+–H···O^- rather than the O–H···N hydrogen bonds. This trend is observed in the present series of complexes as well and hence the observed formation of salt/co-crystal cannot be predicted in terms of ΔpK_a values. Indeed, the ΔpK_a values in the aforesaid complexes are between 0.82 and

Table 3 General details of the molecular complexes[a]

Compound	pK_a	ΔpK_a	Solvent of crystallization	Solvent loss (°C)	Conformations of the OH groups	Salt/co-crystal preferences of the co-formers (CSD)
ML	5.39	—	—	—	—	
1	4.20	1.19	Water	—	—	salt < co-crystal
2	3.01	2.38	Acetonitrile	RT	—	salt > co-crystal
3	4.57	0.82	Water	70–150	—	salt < co-crystal
4	2.96	2.43	Water	<65	*syn–syn* & *syn–anti*	salt < co-crystal
5	3.32	2.07	Water	80–100	*syn–syn*	salt > co-crystal
6	3.01	2.38	Water/DMF	40–100	*syn–syn* & *syn–anti*	salt < co-crystal
7	1.30	4.09	Anhydrous	—	*syn–syn*	salt > co-crystal

[a] The pK_a values of the compounds were obtained from SciFinder.



Scheme 3 Schematic representation of the two distinct topologies observed in the molecular complexes of hydroxyl acids with melamine.

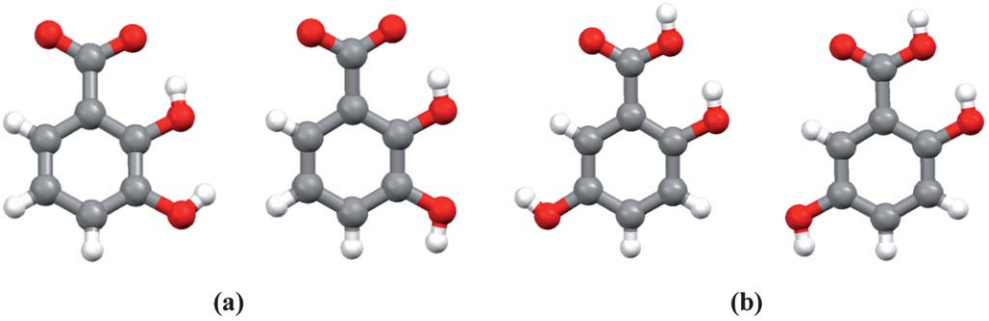


Fig. 8 Conformational variations exhibited by the **DHBA** molecules (a) in **4** and (b) in **6**.

4.09 and therefore a continuum exists between the two extremes (Table 3). A more careful analysis (both theoretical and experimental) of the propensity of salt formation, in terms of energies associated with the hydrogen bonded regions, may provide further insights into the charge transfer mechanism in these complexes.[23]

Conclusions

A series of molecular complexes of **ML** with various hydroxybenzoic acids have been prepared and analyzed, wherein an intricate array of homomeric and heteromeric interactions exist. In the complexes, the hydroxyl and carboxyl groups exhibit a synergic influence in the molecular recognition. Further to the functional groups, topology of the resulting assemblies is influenced by the presence/absence of the solvent of crystallization. Zipper architectures are formed in the hydrated complexes whereas a Lincoln log arrangement is obtained in the presence/absence of other solvents. It is clear that **ML** preferentially forms salts with hydroxy acids and the prediction of proton transfer based on ΔpK_a is inappropriate in these complexes. Database analysis corroborates our claim that in most cases, the recognition of **ML** with carboxylic acids leads to salt formation and the reason for the proton transfer is still elusive. For a quantitative analysis of the salt/co-crystal features, in terms of the charge transfer character at the critical point and acid strengths, a detailed charge density study of the complexes of **ML** with both strong and weak acids is required.

Acknowledgements

TNG thanks DST for the award of a J. C. Bose fellowship and SS thanks UGC for a Dr D. S. Kothari post-doctoral fellowship.

References

1 (*a*) G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311–2327; (*b*) C. B. Aakeröy, *Acta Crystallogr., Sect.B*, 1997, **B53**, 569–586; (*c*) O. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2004, 1889–1896; (*d*) R. Custelcean, M. Vlassa and J. E. Jackson, *Chem.–Eur. J.*, 2002, **8**, 302–308; (*e*) M. W. Hosseini, *Chem. Commun.*, 2005, 5825–5829; (*f*) P. Metrangolo and G. Resnati, *Chem.–Eur. J.*, 2001, **7**, 2511–2519; (*g*) A. Nangia and G. R. Desiraju, *Top. Curr. Chem.*, 1998, **198**, 58–95; (*h*) K. Rissanen, *CrystEngComm*, 2008, **10**, 1107–1113.

2 (*a*) A. D. Bond, *CrystEngComm*, 2007, **9**, 833–834; (*b*) S. Byrn, R. Pfeiffer, G. Stephenson, D. J. W. Grant and W. B. Gleason, *Chem. Mater.*, 1994, **6**, 1148–1158; (*c*) P. Vishweshwar, J. A. McMohan, J. A. Bis and M. J. Zaworotko, *J. Pharm. Sci.*, 2006, **95**, 499–516; (*d*) N. Schultheiss and A. Newman, *Cryst. Growth Des.*, 2009, **9**, 2950–2967; (*e*) A. V. Trask, W. D. S. Motherwell and W. Jones, *Cryst. Growth Des.*, 2005, **5**, 1013–1021; (*f*) D. P. NcNamara, S. L. Childs, J. Giordano, A. Iarriccio, J. Cassidy, M. S. Shet, R. Mannion, E. O'Donnell and A. Park, *Pharm. Res.*, 2006, **23**, 1888–1897; (*g*) S. Karki, T. Friščíc, L. Fábián, P. R. Laity, G. M. Day and W. Jones, *Adv. Mater.*, 2009, **21**, 3905–3909.

3 (*a*) S. Varughese and V. R. Pedireddi, *Tetrahedron Lett.*, 2005, **46**, 2411–2415; (*b*) K. K. Arora, J. PrakashaReddy and V. R. Pedireddi, *Tetrahedron*, 2005, **61**, 10793–10800; (*c*) C. B. Aakeröy, N. Schultheiss and J. Desper, *J. Mol. Struct.*, 2010, **972**, 35–40; (*d*) C. B. Aakeroy, B. M. T. Scott, M. M. Smith, J. F. Urbina and J. Desper, *Inorg. Chem.*, 2009, **48**, 4052–4061; (*e*)

As against 722 hits available for the acid-pyridine heterosynthons there exist only 4 hits for the acid–triazine interaction. The Refcodes corresponding to the acid–triazine interactions are ODEHIO, ROGQUA, WINMIQ and NUSHIT (CSD version 5.32, February 2011 update).

4 (*a*) E. W. Hughes, *J. Am. Chem. Soc.*, 1941, **63**, 1737–1752; (*b*) J. N. Varghese, A. M. O'Connell and E. N. Maslen, *Acta Crystallogr.*, 1977, **B33**, 2102–2108; (*c*) G. J. Perpétuo and J. Janczak, *J. Mol. Struct.*, 2008, **891**, 429–436; (*d*) A. Cousson, B. Nicolai and F. Fillaux, *Acta Crystallogr., Sect. E*, 2005, **E61**, o222–o224.

5 (*a*) A. Ranganathan, V. R. Pedireddi and C. N. R. Rao, *J. Am. Chem. Soc.*, 1999, **121**, 1752–1753; (*b*) A. Ranganathan, V. R. Pedireddi, G. Sanjayan, K. N. Ganesh and C. N. R. Rao, *J. Mol. Struct.*, 2000, **522**, 87–94; (*c*) C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1993, **115**, 905–916.

6 (*a*) http://en.wikipedia.org/wiki/2008_baby_milk_scandal; (*b*) L. Zhu, G. Gamez, H. Chen, K. Chingin and R. Zenobi, *Chem. Commun.*, 2009, 559–561.

7 K. Ai, Y. Liu and L. Lu, *J. Am. Chem. Soc.*, 2009, **131**, 9496–9497.

8 F. H. Allen and O. Kennard, *Chem. Des. Automat. News*, 1993, **8**, 31–37, Refcodes corresponding to the hydrated ML-carboxylic acid complexes; CSD version 5.32, February 2011 update, AJOFUA, ARUDAS, CELHOR, CELHUX, EFAZOA, ETIGUJ, FETTOO, ISUTUL, JIWQIQ, MAQBEM, MAQBIQ, OMIJEZ, QETPIP, ROJGIH, ROJGON, TECFUD, VANDEU, VORSUR, BOPTEG, DUCSOK, TUPKAR.

9 (*a*) M. K. Marchewka, J. Barana, A. Pietraszko, A. Haznar, S. Debrus and H. Ratajczak, *Solid State Sci.*, 2003, **5**, 509–518; (*b*) R. Thomas, S. Pal, A. Datta, M. K. Marchewka, H. Ratajczak, S. K. Pati and G. U. Kulkarni, *J. Chem. Sci.*, 2008, **120**, 613–620; (*c*) K. U. Lakshmi, S. Thamotharan, K. Ramamurthi and B. Varghese, *Acta Crysttallogr., Sect. E.*, 2006, **E62**, o455–o457; (*d*) M. K. Marchewka and A. Pietraszko, *J. Phys. Chem. Solids*, 2003, **64**, 2169–2181; (*e*) H. Su, Y.-K. Lv and Y.-L. Feng, *Acta Crysttallogr., Sect. E.*, 2009, **E65**, o933; (*f*) G. J. Perpetuo and J. Janczak, *J. Mol. Struct.*, 2008, **891**, 429–436.

10 Oxford Diffraction (2009). CrystAlis CCD and CrystAlis RED, Version 1.171.33.31. Oxford Difraction Ltd. Abingdon, Oxfordshire, England.

11 (*a*) G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112–122; (*b*) L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837–838.

12 G. J. Perpetuo and J. Janczak, *Acta Crystallogr., Sect. E*, 2005, **61**, o287–o289.

13 X. Zhang, *Chem. Res. Chin. Univ.*, 2008, **24**, 396–400.

14 R. Ludwig, *Angew. Chem., Int. Ed.*, 2001, **40**, 1808–1827.

15 G. R. Desiraju, *J. Chem. Soc., Chem. Commun.*, 1991, 426–428.

16 (*a*) L. Infantes, J. Chisholm and W. D. S. Motherwell, *CrystEngComm*, 2003, **5**, 480–486; (*b*) L. Infantes, L. Fábián and W. D. S. Motherwell, *CrystEngComm*, 2007, **9**, 65–71; (*c*) L. Infantes and W. D. S. Motherwell, *Z. Kristallogr.*, 2005, **220**, 333–339.

17 H. D. Clarke, K. K. Arora, H. Bass, P. Kavuru, T. T. Ong, T. Pujari, L. Wojtas and M. J. Zaworotko, *Cryst. Growth Des.*, 2010, **10**, 2152–2167.

18 S. Varughese and G. R. Desiraju, *Cryst. Growth Des.*, 2010, **10**, 4184–4196.

19 (*a*) S.-P. Chen, M. Li, Y. Xuao, Y.-X. Yuan, L.-L. Pan and L.-J. Yuan, *CrystEngComm*, 2008, **10**, 1227; (*b*) L. E. Cheruzel, M. S. Pometun, M. R. Cecil, M. S. Mashuta, R. J. Wittebort and R. M. Buchanan, *Angew. Chem., Int. Ed.*, 2003, **42**, 5452; (*c*) Z. Fei, D. Zhao, T. J. Geldbach, R. Scopelliti, P. J. Dyson, S. Antonijevic and G. Bodenhausen, *Angew. Chem., Int. Ed.*, 2005, **44**, 5720; (*d*) U. S. Raghavender, A. Kantharaju, S. Aravinda, N. Shamala and P. Balaram, *J. Am. Chem. Soc.*, 2010, **132**, 1075; (*e*) A. Wakahara and T. Ishida, *Chem. Lett.*, 2004, **33**, 354; (*f*) A. Wu, Y. Li, F. Zheng, G. Guo and J. Huang, *Cryst. Growth Des.*, 2006, **6**, 444.

20 K. Murata, K. Mitsuoka, T. Hirai, T. Walz, P. Agre, J. B. Heymann, A. Engel and Y. Fujiyoshi, *Nature*, 2000, **407**, 599–605.

21 (*a*) S. L. Childs, G. P. Stahly and A. Park, *Mol. Pharmaceutics*, 2007, **4**, 323–338; (*b*) C. B. Aakeroy, M. E. Fasulo and J. Desper, *Mol. Pharmaceutics*, 2007, **4**, 317–322; (*c*) S. Mohamed, D. A. Tocher, M. Vickers, P. G. Karamertzanis and S. L. Price, *Cryst. Growth Des.*, 2009, **9**, 2881–2889; (*d*) K.-S. Huang, D. Britton, M. C. Etter and S. R. Byrn, *J. Mater. Chem.*, 1997, **7**, 713–720; (*e*) B. R. Bhogala, S. Basavoju and A. Nangia, *CrystEngComm*, 2005, **7**, 551–562.

22 S. L. Johnson and K. A. Rumon, *J. Phys. Chem.*, 1965, **69**, 74.

23 V. R. Hathwar, R. Pal and T. N. G. Row, *Cryst. Growth Des.*, 2010, **10**, 3306–3310.

