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Multicomponent Solvate Crystals of 3,5-Dinitrobenzoic Acid and Acetamide and CSD Analysis of Solvates

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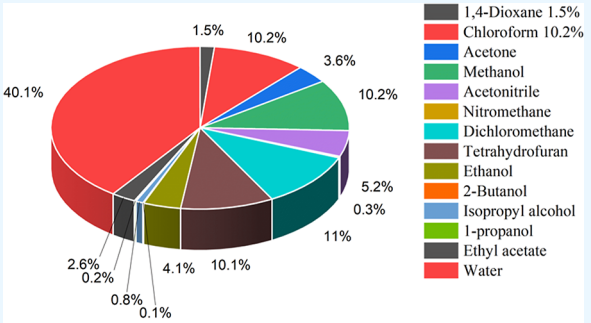
ABSTRACT: Twelve multicomponent solvate crystals (cocrystal solvates) of 3,5-dinitrobenzoic acid and acetamide were synthesized via slow evaporation method. All crystalline materials were characterized by single-crystal X-ray diffraction. All cocrystal solvates are isostructural, and crystal packing forms continuous channels where some solvent molecules are connected via weak intermolecular interactions with 3,5-dinitrobenzoic acid and acetamide. All multicomponent solvate crystals encompass amide−amide dimer homo synthons and form R_2^2 (8) motifs. Moreover, the phase purity of solvate crystals was analyzed by powder X-ray diffraction. Further, most of the cocrystal solvates were analyzed by nuclear magnetic resonance and differential scanning calorimetry. Cambridge structural database analysis categorizes solvate propensity in single-crystal structures. The importance of hydrogen bond donor/acceptor nature, size, and shape of solvents is also discussed in the context of crystallization and crystal packing.



CSD analysis: Solvates propensity in the crystal structures.

INTRODUCTION

Crystal engineering[1,2] is about understanding intermolecular interactions in single-component and multicomponent molecular crystals.[3,4] Multicomponent crystals[5−7] can be synthesized by the supramolecular synthon[8] approach and shape and size mimicry.[9,10] Cocrystals, salts, solvates, cocrystal salts, salt solvates, cocrystal solvates,[11] and cocrystal salt solvates are characterized under the category of multicomponent crystals.[5,12,13] If water is occupied in the crystalline lattice, it is called hydrate or hydrated crystals.[14−21] If the asymmetric unit contains at least one solvent molecule along with the API and/or given molecule, the crystal is called a solvate crystal. In another scenario, multicomponent crystalline solids can be described as host−guest complexes,[22] clathrates,[23] and pseudo polymorphs.[24−27] The phenomenon of the host−guest system has a fundamental importance in pharmaceutical drug development,[28] so the study of model compounds well in advance could be advantageous. Recently, Desiraju's group designed a host−guest system of hydrated 3,5-dihydroxybenzoic acid where water was used as a design element.[15] Mostly, the isostructural host−guest system ends up with similar crystal packing, and guests are occupied at the same site.[29,30] Very recently, we reported isostructural organic salt alloys of naftopidil and aromatic carboxylic acids where binary salts are formed with R_2^2 (9) motifs.[31] In some cases, solvents play a crucial role in the change of organic framework and crystal habit.[32−36] Solvents also can affect polymorphism in crystallization.[37−39] Recently, we also studied the importance of solvents in forming polymorphs in single-component crystals of triclabendazole[40] and cocrystal polymorphs of urea-4,4-bipyridine.[41] In solvent-induced polymorphs, solvent directs the crystalline material without the appearance of solvents in the crystalline lattice.[41] In another case, solvents can be seen along with the given crystalline material; for instance, solvate of 4-hydroxy benzoic acid[42] and cocrystal solvates of triclabendazole.[40] In another example, ethenzamide and 3,5-dinitrobenzoic acid formed isostructural solvate cocrystals.[43] In another recent study of cocrystal solvates, it showed improvement in the solubility of APIs.[44] In the broad classification of crystalline materials, solvate crystals have some significance and their own identity. To understand the role of solvents in crystallization and crystal packing, here we have studied 3,5-dinitrobenzoic acid−acetamide solvates (multicomponent crystals), such as 3,5-dinitrobenzoic acid−acetamide 1,4-dioxane (**1**), 3,5-dinitrobenzoic acid−acetamide $CHCl_3$ (**2**), 3,5-dinitrobenzoic acid−acetamide acetone (**3**), 3,5-dinitrobenzoic acid−acetamide MeOH (**4**), 3,5-dinitrobenzoic acid−acetamide CH_3CN (**5**), 3,5-dinitrobenzoic acid−acetamide CH_3NO_2 (**6**), 3,5-dinitrobenzoic acid−acetamide DCM (**7**), 3,5-dinitrobenzoic acid−acetamide−THF (**8**) 3,5-dinitrobenzoic acid−acetamide EtOH (**9**), 3,5-dinitrobenzoic acid−acetamide−isopropyl alcohol (**10**), 3,5-

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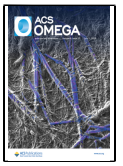
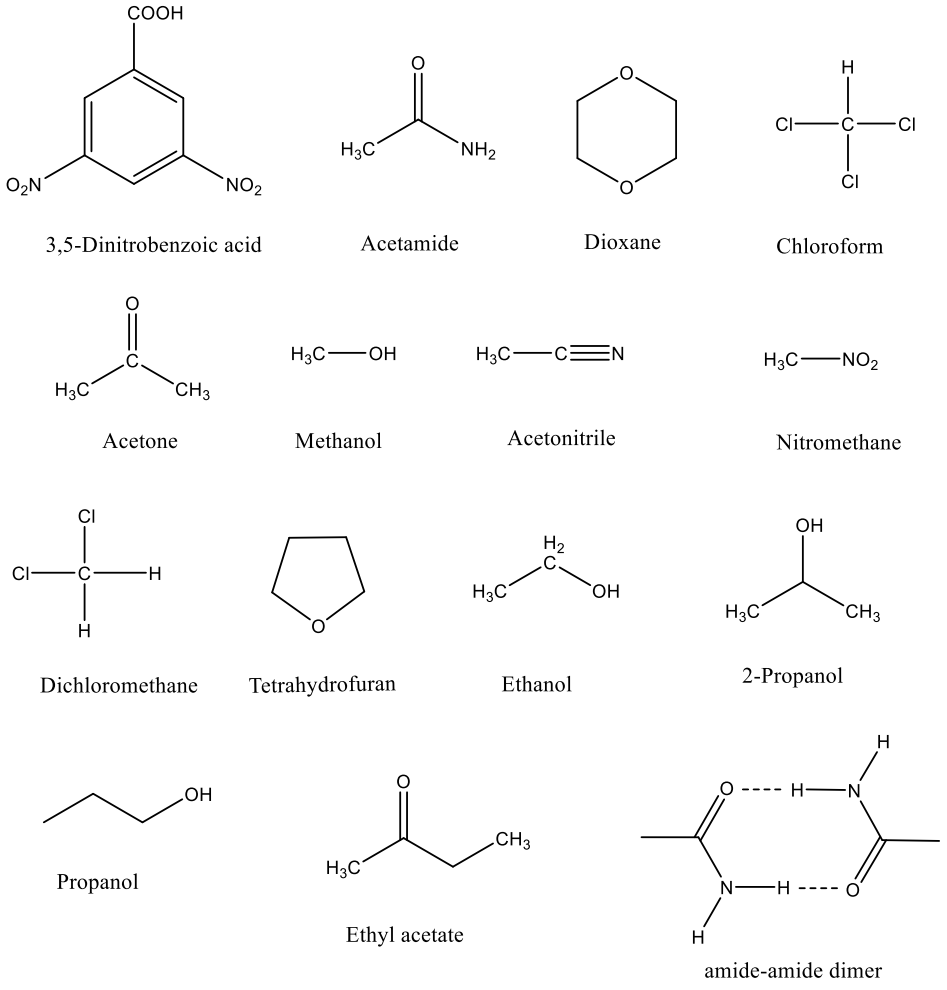


Scheme 1. Molecules Are Used for Multicomponent Solvate Crystals (Cocrystal Solvates)[a]



[a]The basic supramolecular synthon in the crystal structure can be seen at the end.

dinitrobenzoic acid−acetamide−propanol (**11**), and 3,5-dinitrobenzoic acid−acetamide−ethyl acetate (**12**) (Scheme 1 and Table 1).

EXPERIMENTAL SECTION

Materials and Methods. 3,5-Dinitrobenzoic acid and acetamide were purchased from TCI chemicals. Solvents were purchased from local suppliers (Thomas Baker) and used as such without further purification.

Table 1. Cocrystal Solvates and Their Codes

sr. no	cocrystal solvates	
1	3,5-dinitrobenzoic acid−acetamide−1,4-dioxane	**1**
2	3,5-dinitrobenzoic acid−acetamide−chloroform	**2**
3	3,5-dinitrobenzoic acid−acetamide−acetone	**3**
4	3,5-dinitrobenzoic acid−acetamide−methanol	**4**
5	3,5-dinitrobenzoic acid−acetamide−acetonitrile	**5**
6	3,5-dinitrobenzoic acid−acetamide−nitromethane	**6**
7	3,5-dinitrobenzoic acid−acetamide−dichloromethane	**7**
8	3,5-dinitrobenzoic acid−acetamide−tetrahydrofuran	**8**
9	3,5-dinitrobenzoic acid−acetamide−ethanol	**9**
10	3,5-dinitrobenzoic acid−acetamide−isopropyl alcohol	**10**
11	3,5-dinitrobenzoic acid−acetamide−propanol	**11**
12	3,5-dinitrobenzoic acid−acetamide−ethyl acetate	**12**

Cocrystallization. 0.1 mmol of 3,5-dinitrobenzoic acid and acetamide were taken in 15 mL vials, and 12 such samples were prepared. Later, 3−5 mL of 12 different solvents were added separately. The reaction mixture was gently heated to make a homogeneous solution. The crystallization mixture was kept for slow evaporation at R.T. Good quality single crystals were obtained in 3−7 days.

X-ray Crystallography. **1**, **3**, **4**, **5**, **6**, **8**, **10**, and **11** cocrystal solvates were collected on a Rigaku Mercury 375/M CCD (XtaLAB mini) diffractometer using graphite monochromated Mo-Kα radiation at 150 K/213 K/293 K. Rigaku crystal clear software[45] was used for processing the data. **2**, **7**, **9**, and **12** cocrystal solvates were mounted on a Bruker SMART APEX II single-crystal X-ray CCD diffractometer having graphite monochromatized (Mo-Kα = 0.71073 Å) radiation at a low temperature of 100 K. A X-ray generator was operated at 50 kV and 30 mA. The X-ray data acquisition was monitored by the APEX2 program suit. The data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs which are an integral part of the APEX2 package.[46] The structures were solved by direct methods and refined by full-matrix least-squares, based on F^2, using SHELXL.[47] Crystal structures were refined using Olex2-1.0 software.[48] Anisotropic refinement was performed for all non-H atoms. Most of the hydrogen atoms attached to hetero

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atoms were located through a difference in the Fourier map, and some O−H hydrogen atoms were geometrically fixed using the HFIX command in SHELXL. All hydrogen atoms are refined isotropically. The structures were examined using the ADSYM subroutine of PLATON[49] to assure that no additional symmetry could be applied to the models. Mercury software was used to prepare packing diagrams and molecular interactions. Crystallographic.cif files (CCDC nos. 1880081−1880086 and 1880088−1880093) are available at www.ccdc.cam.ac.uk/data. ORTEP diagrams and packing indexes are shown in the Supporting Information, Section S2.

Powder X-ray Diffraction. All crystalline material powder X-ray diffraction (PXRD) patterns were recorded on a Rigaku Smartlab diffractometer for Cu Kα radiation (λ= 1.5406 Å), with a scan speed of 2° min^{-1} and a step size of 0.02° in 2θ. All crystalline samples were scanned over a range of 2θ = 5−40°.

Nuclear Magnetic Resonance Experimental Section. Some cocrystal solvate solution-state nuclear magnetic resonance (NMR) experiments were performed in methanol-d4 on 400 MHz Bruker AVANCE spectrometers equipped with a triple resonance probe. The sample temperature was regulated to 298 ± 2 K. All spectra were a reference to the respective solvent as a standard. ^{1}H NMR spectra were acquired using a single pulse with a relaxation delay of 3 s. Some 1D-^{1}H NMR experiments for the individual components and cocrystal solvates are recorded in DMSO-d_6 at 298 K on a Bruker Avance 200 MHz NMR spectrometer equipped with 5 mm DUL ^{13}C−^{1}H/^{2}H Z8243/007. Solvents in the solvated cocrystals were identified by careful analysis of chemical shifts.[50]

Differential Scanning Calorimetry Analysis. Differential scanning calorimetry (DSC) analysis for cocrystal solvates was carried out on a Mettler Toledo Instrument (DSC822) Artesyn Technologies. 5−8 mg crystals were taken in an Al_2O_3 pan, and the heating rate was set to about 10 °C/min and the sample was heated from R.T. to 350 °C.

Thermogravimetric Analysis. Thermogravimetric analysis (TGA) for cocrystal solvates was carried out on a NETZSCH TG 209F1 Libra TGA209F1D-0105-L. 5−8 mg crystals were taken in an Al_2O_3 crucible, and the heating rate was set to about 10 °C/min and the sample was heated from R.T. to up 800 °C.

Cambridge Structural Database Analysis. All solvents were drawn in the ConQest1.20 software[51] and searched for the number of solvated crystals in the Cambridge structural database (CSD). Filters such as 3D coordinates determined no errors, not polymorphic, no ions/ionic, only single-crystal structures, and only organics were used (CSD version 5.43 with March and June updates).

RESULTS AND DISCUSSION

Multicomponent crystals can act as host systems for numerous solvents. We synthesized 12 multicomponent crystal solvates of 3,5-dinitrobenzoic acid and acetamide. Molecules are stabilized by amide−amide homo synthons of the R_2^2 (8) motif, which is further connected to acid via the O−H···O hydrogen bond (Figure 1) in all crystal structures. Twelve crystal structures are categorized in two ways. In the first case, solvents are ordered in the crystalline lattice (1,4-dioxane, acetone, and $CHCl_3$) (Figure 2). In the second case, solvents are disordered. Hence, those are squeezed (isopropyl alcohol, propanol, THF, MeOH, EtOH, nitromethane, acetonitrile, EtOAc, and DCM). A ^{1}H NMR characterization technique was used to identify the solvent present in the crystalline lattice.

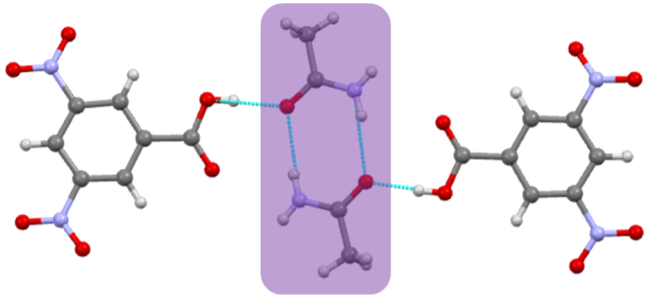

Figure 1. Basic supramolecular synthon (amide−amide dimer) in the crystal packing of all single crystal structures of 3,5-dinitrobenzoic acid acetamide solvates. Note that it is further connected via the O−H···O hydrogen bond.

Single-Crystal Structure Data. 3,5-Dinitrobenzoic acid−acetamide−1,4-dioxane solvate cocrystal (**1**): crystallized $P2_12_12$ space group with two molecules of 3,5-dinitrobenzoic acid and acetamide and half molecule of 1,4-dioxane in the asymmetric unit. Molecules are associated together with the amide−amide dimer, which is further connected to the acid via the O−H···O hydrogen bond (Figure 1). This pattern can also be seen in cocrystal solvates of ethenzamide and 3,5-dinitrobenzoic acid.[43] The role of acetamide in 3,5-dinitrobenzoic acid and acetamide cocrystal solvates is similar to ethenzamide in cocrystal solvates of ethenzamide and 3,5-dinitrobenzoic acid. In the crystal packing diagram of 3,5-dinitrobenzoic acid and acetamide-1,4-dioxane solvate, 1,4-dioxane occupies the center and corner of the unit cell (Figure 3a). The crystallographic data can be seen in Table 2.

3,5-Dinitrobenzoic acid−acetamide $CHCl_3$ solvate cocrystals (**2**) has a $P2_12_12$ space group and the packing is similar to earlier structures. $CHCl_3$ is disordered, and one of the chlorine atoms sits on a 2-fold axis. The crystal packing forms continuous channels along the *c*-axis, and $CHCl_3$ can be seen along channels (Figure 3b).

3,5-Dinitrobenzoic acid−acetamide−acetone solvate cocrystal (**3**): like the earlier solvated crystal, it also has a $P2_12_12$ space group. In the asymmetric unit, half a molecule of acetone and two molecules of 3,5-dinitrobenzoic acid and acetamide were observed. Basic supramolecular synthons are the same as an earlier solvate. Acetone molecules form channels along the *c*-axis and any two consecutive acetone molecules run in an antiparallel direction (Figure 3c). Crystal packing diagrams of multicomponent crystals (cocrystal solvates) are shown in Figure 3.

3,5-Dinitrobenzoic acid−acetamide solvates (**4**−**12**) form a similar type of crystal packing (Figure 4). The channels have many diffused electron densities, so the solvent mask is used in the structure solution and refinement. If the solvent is removed from the crystalline lattice, continuous channels can be seen along the *c*-axis. Those channels can also be viewed from the *b* and *a*-axes (Figure 4). Disordered solvated multicomponent crystals were investigated through ^{1}H NMR. The primary pore diameter is 6.45 Å along the *c*-axis (Figure 5). There are two such pore channels in the unit cell. If molecules are viewed along the *c*-axis, the arrangement of molecules looks like the ABAB type. Two consecutive layers of 3,5-dinitrobenzoic acid run in the opposite direction and are slightly sheared halfway along the *c*-axis. When the solvents are removed, the unit cells

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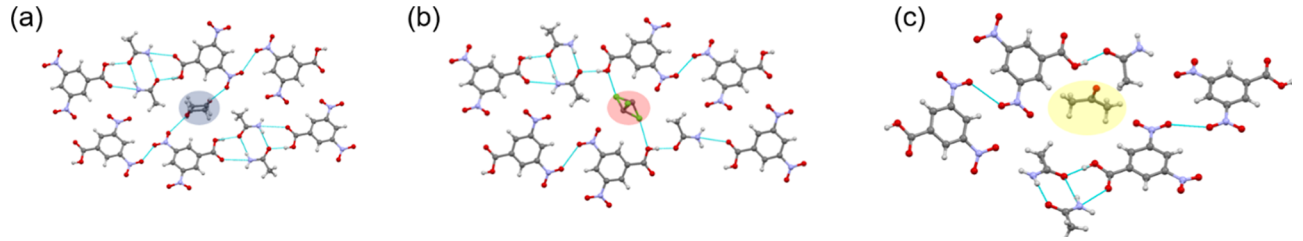

Figure 2. Multicomponent solvate crystals (cocrystal solvates) of 3,5-dinitrobenzoic acid acetamide (a) 1,4-dioxane, (b) chloroform, and (c) acetone.

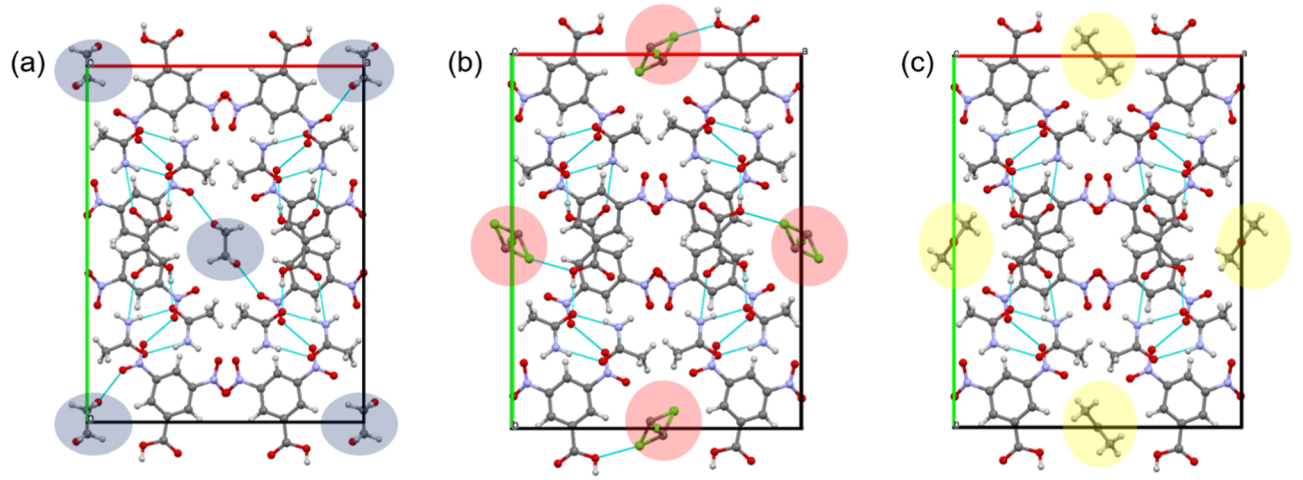

Figure 3. Packing diagram of multicomponent solvate crystals (cocrystal solvates) of 3,5-dinitrobenzoic acid acetamide (a) 1,4-dioxane, (b) chloroform, and (c) acetone.

of crystal structures show a 9.9−10.8% void space in the entire unit cells. In general, solvents used for crystallization play a crucial role in the formation of single crystals and also polymorphs. The solvent occupies the crystalline lattice to compensate for the complementary donor−acceptor ratio or stabilize crystal packing by occupying vacant sites such as voids. The type of solvents that occupy the crystal lattice usually depends on the size and shape of the solvent to the void. If the framework is stable, it could separate the mixture of solvents and design new multicomponent solid forms. In all solvates, R_2^2 (8) motif is common, and D_2^2 (6)/D_2^2 (5) motifs are also seen in solvates like **1**, **2**, and **3**. Here, the discrete chain is formed with two donors and two acceptors. In **4**, C_2^2 (12) chain motifs are formed between 3,5-dinitrobenzoic acid, acetamide, and 3,5-dinitrobenzoic acid. Discrete chain motifs D_3^2 (7) and D_3^3 (9) are formed with two acids and two amides. In other crystal structures (**4**−**12**), crystal packing is formed with similar synthons, so the motifs as mentioned earlier are observed.

PXRD Analysis. Single-crystal data shows that all multicomponent solvate crystals (cocrystal solvates) are isostructural. PXRD of single component crystals (3,5-dinitrobenzoic acid and acetamide) is compared with the crystalline material obtained from cocrystallization of 3,5-dinitrobenzoic acid and acetamide (Figure 6 and Table 3). PXRD of **1**, **2**, and **3** multicomponent solvate cocrystals show a similar pattern. However, the slight difference arises only due to the solvent occupied in the channel (Figure 7). Later, all remaining multicomponent solvate crystals are compared with native components, and it is clear that most patterns have similar peak positions; hence, essential crystal packing would be the same. This particular study can be correlated with a recent survey on quasi-racemic cage−cage cocrystals where all crystalline material PXRD patterns appear similar with a shifting of peak position.[52] Then, it was correlated that as the size of the cage increases (*d*-spacing), there is a decrease in the 2θ value in the PXRD pattern. In the current study, we also compared simulated PXRD patterns with experimental PXRD patterns, and all peak positions match, which implies that the bulk crystalline material is in the phase pure Figure 8. PXRD data of other solvated cocrystals can be seen in Supporting Information, Section S1. In addition, ORTEP diagrams are shown in Supporting Information, Section S2.

NMR. In general, single-crystal X-ray diffraction (SCXRD) is a good characterization technique to identify the exact stoichiometry in a given crystalline material. If a single crystal contains a solvent with diffused electron density, it is difficult to model the solvent. So the ^{1}H NMR study was used to characterize multicomponent solvate crystals (cocrystal solvates). This particular research aims to investigate solvents in the crystalline lattice of a given crystal. ^{1}H NMR spectra of 3,5-dinitrobenzoic acid show proton peaks at 9.085−9.169 ppm (highlighted with orange) in the aromatic region. In ^{1}H NMR spectra, the methyl group of acetamide (CH_3CONH_2) shows a peak at 1.927 ppm (highlighted with purple color). Moreover, the solvent in the crystalline lattice is highlighted with a red color (2.024 ppm for acetonitrile), as shown in Figure 9. For other spectra analyses of other samples, we used the same color code (Supporting Information, Section S3). Moreover, TGA and DSC are shown in Supporting Information, Section S4.

CSD Analysis of Solvates. Solvents play a crucial role in the formation of single crystals for diffraction studies.

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Table 2. Crystallographic Table of Multicomponent Solvate Crystals

	1	2	3	4	5
sum formula	$C_{20}H_{22}N_6O_{15}$	$C_{37}H_{36}Cl_3N_{12}O_{28}$	$C_{39}H_{42}N_{12}O_{29}$	$C_9H_9N_3O_7$	$C_9H_9N_3O_7$
formula weight	586.4	1203.13	1142.85	271.19	271.19
crystal system	orthorhombic	orthorhombic	orthorhombic	orthorhombic	orthorhombic
space group	$P2_12_12$	$P2_12_12$	$P2_12_12$	*Pccn*	*Pccn*
a (Å)	17.041(3)	16.9931(12)	17.032(3)	17.009(3)	17.051(3)
b (Å)	21.935(4)	21.9038(15)	21.944(4)	21.921(4)	21.941(4)
c (Å)	6.7247(13)	6.6422(4)	6.6910(13)	6.6780(13)	6.7580(14)
V (Å^3)	2513.7(8)	2472.3(3)	2500.8(8)	2489.9(8)	2528.3(8)
D_{calc} (g cm^{-3})	1.550	1.616	1.518	1.447	1.425
Z	4	2	2	8	8
F(000)	1216.0	1234.0	1184.0	1120.0	1120.0
residual electron density $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	−0.43 to 0.52 e Å^{-3}	−0.31 to 0.26 e Å^{-3}	−0.38 to 0.69 e Å^{-3}	−0.60 to 0.54 e Å^{-3}	−0.50 to 0.52 e Å^{-3}
h range	22	21	22	22	22
k range	28	27	28	28	28
l range	8	8	8	8	8
measured reflections	26,693	47,568	26,128	24,352	25,020
independent reflections	5762	5066	5706	2859	2905
reflections with $I > 2\sigma(I)$	5522	5034	5382	2296	2384
R_{int}	0.079	0.024	0.048	0.102	0.064
R_1 [$I > 2\sigma(I)$]	0.053	0.021	0.051	0.068	0.077
wR_2 (all)	0.1612	0.0591	0.1592	0.2033	0.2085
goodness of fit	1.106	1.073	1.092	1.152	1.391
CCDC no	1880081	1880083	1880082	1880084	1880089
	6	**7**	**8**	**9**	**10**
sum formula	$C_9H_9N_3O_7$	$C_9H_9N_3O_7$	$C_9H_9N_3O_7$	$C_9H_9N_3O_7$	$C_9H_9N_3O_7$
formula weight	271.19	271.19	271.19	271.19	271.19
crystal system	orthorhombic	orthorhombic	orthorhombic	orthorhombic	orthorhombic
space group	*Pccn*	*Pccn*	*Pccn*	*Pccn*	*Pccn*
a (Å)	17.024(3)	16.9109(16)	17.150(3)	16.9418(6)	17.107(3)
b (Å)	21.893(4)	21.9079(19)	21.985(4)	21.8913(7)	21.898(4)
c (Å)	6.6837(11)	6.6123(7)	6.6977(11)	6.6056(2)	6.8180(14)
V (Å^3)	2491.1(8)	2449.7(4)	2525.3(8)	2449.87(14)	2554.1(8)
D_{calc} (g cm^{-3})	1.446	1.471	1.427	1.470	1.411
Z	8	8	8	8	8
F(000)	1120.0	1120.0	1120.0	1120.0	1120.0
residual electron density $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	−0.58 to 0.64 e Å^{-3}	−0.28 to 0.46 e Å^{-3}	−0.25 to 0.29 e Å^{-3}	−0.23 to 0.30 e Å^{-3}	−0.59 to 0.56 e Å^{-3}
h range	22	24	22	21	22
k range	28	31	28	27	28
l range	8	9	8	8	8
measured reflections	23,533	171,517	24,870	61,240	24,866
independent reflections	2834	3746	2917	2493	2948
reflections with $I > 2\sigma(I)$	2538	3573	2557	2427	2533
R_{int}	0.121	0.042	0.103	0.024	0.055
R_1 [$I > 2\sigma(I)$]	0.073	0.034	0.071	0.032	0.073
wR_2 (all)	0.2035	0.0919	0.2002	0.0959	0.2278
goodness of fit	1.228	1.066	1.257	1.127	1.224
CCDC no	1880086	1880092	1880085	1880091	1880088

	11	12
sum formula	C_9 H_9 N_3 O_7	$C_9H_9N_3O_7$
formula weight	271.19	271.19
crystal system	orthorhombic	orthorhombic
space group	*Pccn*	*Pccn*
a (Å)	17.039(2)	17.020(2)
b (Å)	21.918(3)	21.891(3)
c (Å)	6.6903(9)	6.6224(9)
V (Å^3)	2498.6(6)	2467.4(6)
D_{calc} (g cm^{-3})	1.442	1.460
Z, *Z*′	8, 1	8, 1
F(000)	1120.0	1120.0

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Table 2. continued

	11	12
residual electron density $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	−0.33 to 0.39 e Å^{-3}	−0.24 to 0.29 e Å^{-3}
h range	22	21
k range	28	27
l range	8	8
measured reflections	24,414	60,147
independent reflections	2865	2499
reflections with $I > 2\sigma(I)$	2707	2465
R_{int}	0.145	0.026
R_1 [$I > 2\sigma(I)$]	0.055	0.039
wR_2 (all)	0.1748	0.0914
goodness of fit	1.222	1.159
CCDC no	1880090	1880093

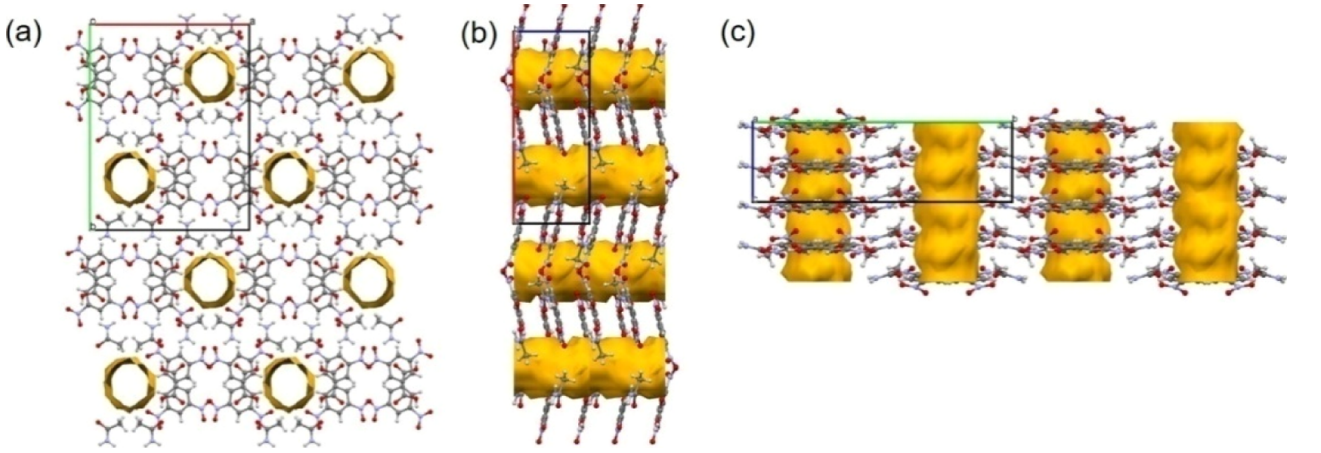

Figure 4. Solvent channels in the multicomponent solvate crystals (cocrystal solvates) of 3,5-dinitrobenzoic acid acetamide (a) *c*-axis, (b) *b*-axis, and (c) *a*-axis.

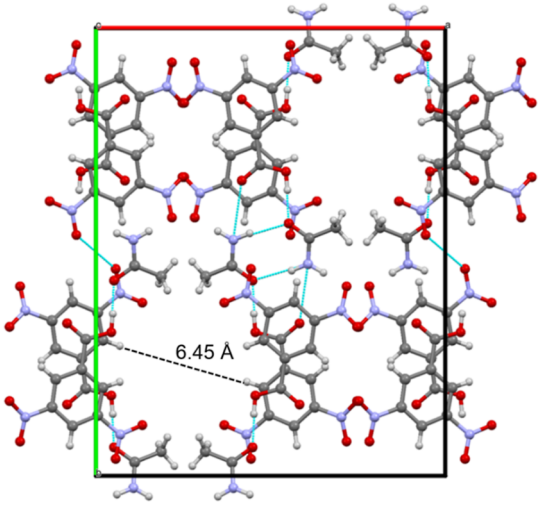

Figure 5. Basic packing diagram of all multicomponent solvate crystals (cocrystal solvates) of 3,5-dinitrobenzoic acid acetamide. The solvent is not correctly ordered in the crystal packing.

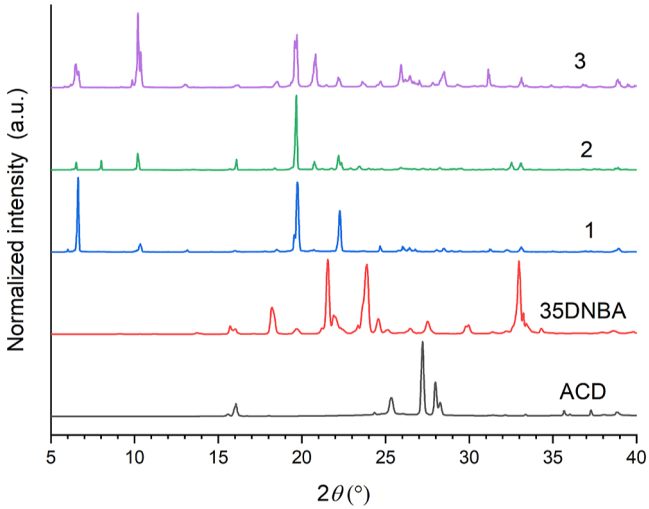

Figure 6. PXRD comparison of native compounds 3,5-dinitrobenzoic acid (35DNBA) acetamide (ACD) with multicomponent cocrystal solvates of **1**, **2**, and **3**.

Sometimes solvents used for crystallization appear in the crystalline lattice. In general, water occupies the lattice when donors are insufficient in hydrogen bond formation. Other factors include size, shape, and position of donor/acceptor in the molecule. By careful CSD analysis (Table 4), hydrate (water) crystals dominate other solvates with the highest number of hits (20,988). Among different solvates, DCM, THF, and MeOH lead other solvents; this is because, during crystallization, crystal packing might end up with small voids, which are good enough to accommodate small molecules like THF and MeOH. In addition, those molecules act as good acceptors and donors, respectively. Fewer hits are noted for other solvents due to the size of the void not being suitable or poor donor/acceptor capability. In the case of CH_2Cl_2 and

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Table 3. PXRD Pattern of Single Component Crystals and Multicomponent Cocrystal Solvates

	sr. no	ACD	35DNBA	1	2	3
2θ characteristic peak positions	1	15.58	13.72	6.01	6.52	5.81
	2	16.06	15.72	6.63	8.01	6.20
	3	24.33	16.00	10.34	10.19	6.51
	4	25.32	18.02	13.16	16.09	6.66
	5	27.22	19.70	15.98	18.38	9.87
	6	27.98	21.00	18.50	19.67	10.20
	7	28.26	21.55	19.54	20.75	10.36
	9	33.37	21.91	19.73	22.20	13.00
	10	35.70	23.36	20.70	22.32	16.10

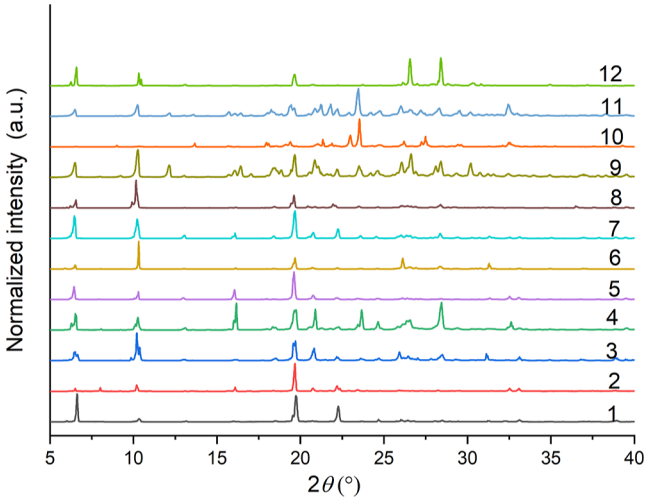

Figure 7. PXRD comparison of multicomponent solvate crystals (cocrystal solvates) of 3,5-dinitrobenzoic acid acetamide.

$CHCl_3$, molecules are almost spherical, so their lattice can be adjusted easily; hence, a decent number of solvate crystals are observed in the CSD. Concerning acetonitrile, it is a linear and small molecule, so it could easily fit if there is a small vacancy in the crystal lattice. Moreover, ethanol can act as a good donor and acceptor; therefore, it stands almost in the middle of the hierarchy of solvate crystals. In the case of isopropyl alcohol, 2-butanol molecular size is more extensive and not spherical, so fewer hits are present in the CSD. Solvate propensity in the crystal structures is shown in Figure 10.

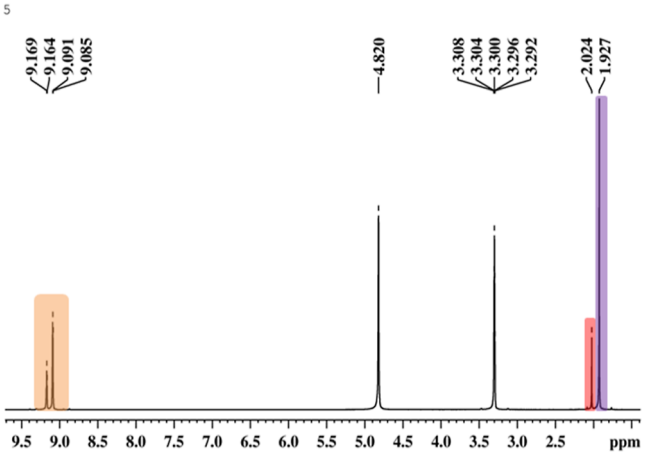

Figure 9. ^{1}H NMR spectrum of 3,5-dinitrobenzoic acid−acetamide−acetonitrile solvate cocrystal. It was recorded in the methanol-d_4 solvent. 3,5-dinitrobenzoic acid and acetamide protons are highlighted with orange and violet, respectively. 2.0 ppm (highlighted in red) peak corresponds to ACN in the crystal lattice. 4.8 and 3.3 ppm correspond to the solvent residual peak (water) and methanol-d_4 solvent.

Table 4. CSD Analysis of Solvates

sr no	solvent	solvates
1	1,4-dioxane (DXN)	807
2	chloroform ($CHCl_3$)	5330
3	acetone (ACTN)	1890
4	methanol (MeOH)	5350
5	acetonitrile (CH_3CN)	2711
6	nitromethane ($MeNO_2$)	147
7	dichloromethane (DCM)	5738
8	tetrahydrofuran (THF)	5272
9	ethanol (EtOH)	2143
10	isopropyl alcohol (IPA)	422
11	1-propanol (PROP)	97
12	ethyl acetate (EAT)	1379
13	2-butanol (BuOH)	42
14	water (H_2O)	20,988

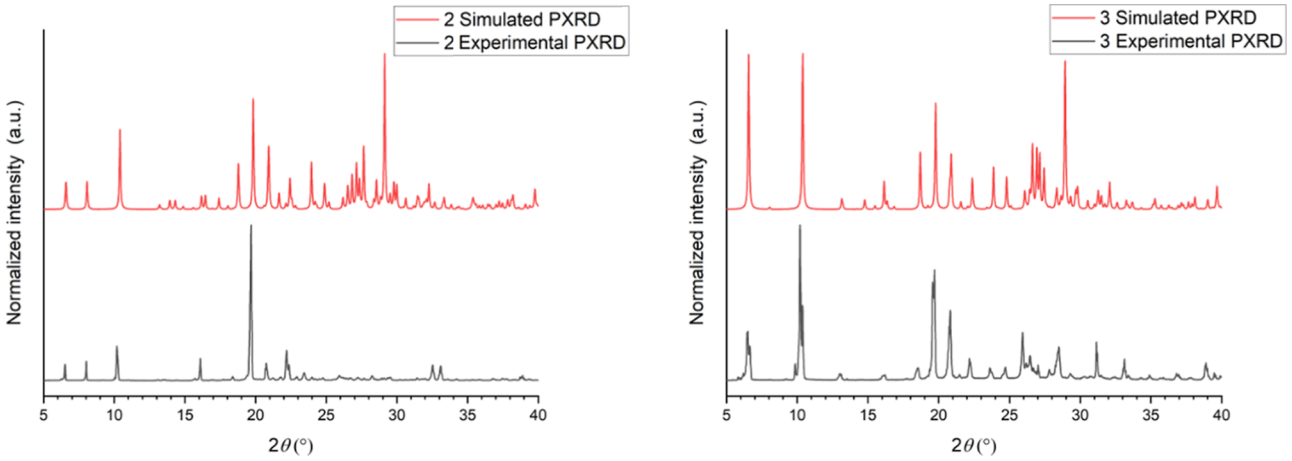

Figure 8. Experimental and simulated PXRD of multicomponent solvate crystals (cocrystal solvates) of **2** and **3** all other data are given in the Supporting Information.

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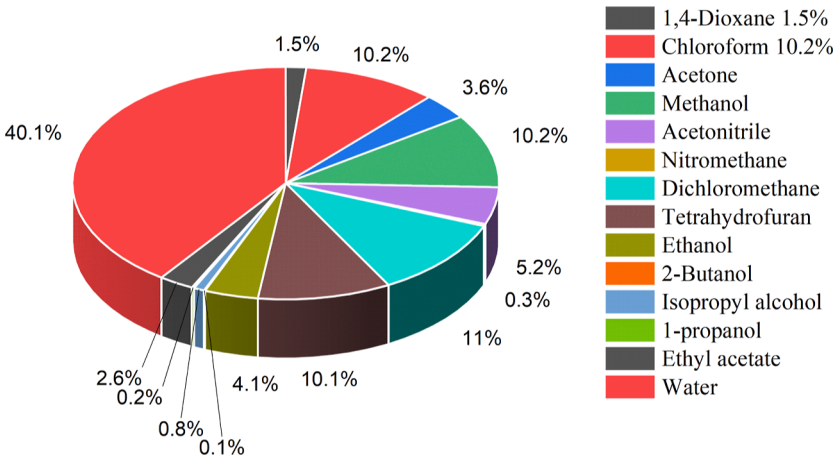

Figure 10. CSD analysis: solvate propensity in the crystal structures.

CONCLUSIONS

We systematically synthesized 12 multicomponent single-crystal structures of 3,5-dinitrobenzoic acid acetamide solvates. Crystal packing of multicomponent solvate crystal has continuous channels along the *c*-axis. In a few cases, for instance, 1,4-dioxane, acetone, and $CHCl_3$ are well ordered, so those molecules are located in the crystalline lattice by SCXRD data. In other multicomponent solvated crystals (isopropyl alcohol, propanol, THF, MeOH, EtOH, nitromethane, and acetonitrile), electron density is diffused, so solvents in the crystalline lattice were characterized by ^{1}H NMR. All multicomponent solvate crystals have a R_2^2 (6) motif, which is further connected to acid via the O−H···O hydrogen bond. Using CSD, we rationalized solvent manifestation in the crystal structures by considering solvents' size, shape, and donor−acceptor propensity. Currently, we are trying to stabilize the host framework of 3,5-dinitrobenzoic acid and acetamide solvates. Later, it will be used as the host system to synthesize new multicomponent solid forms.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03091.

PXRD data, ORTEP diagrams, ^{1}H NMR plots, TGA, and DSC plots of multicomponent solvates (cocrystal solvates) (PDF)

Crystallographic information files (CIFs) (ZIP)

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Notes

The authors declare no competing financial interest.

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