Combinations of Tautomeric Forms and Neutral-Cationic Forms in the Cocrystals of Sulfamethazine with Carboxylic Acids

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Supporting Information

ABSTRACT: The cocrystals of sulfamethazine with different acids, namely, 2-mercaptophenylcarboxylic acid, 2,6-pyridinedicarboxylic acid, 4-(4-hydroxyphenylazo)phenylcarboxylic acid, 3-(4-hydroxyphenyl)propanoic acid, and 4-(phenyl)phenylcarboxylic acid, are studied here. Each has distinct notable supramolecular features. The pyrimidin-2-amine unit of the sulfamethazine provided unique examples of cocrystals in which amidine and imidine forms or neutral and protonated forms of sulfamethazine are observed in 2:2 ratios. Hence, this study provides avenues to explore cocrystals with tautomeric forms together in a cocrystal and also neutral and protonated cocrystal partners as apparent multicomponents in cocrystals. Among the cocrystals, three of them have the amidine form of the sulfamethazine in respective self-assembly. The cocrystal of 2-mercapto-phenylcarboxylic acid with sulfamethazine has the amidine form and it has the distinction of having S−H⋯π interactions. The cocrystal of sulfamethazine with 2,6-pyridinedicarboxylic acid is a rare example of a 1:1 cocrystal of sulfamethazine with dicarboxylic acid. It has methanol molecules as a solvent of crystallization. Sulfamethazine forms a hydrated cocrystal with 4-(4-hydroxyphenylazo)-phenylcarboxylic acid that has conventional \( R_2^2(8) \) synthons of amidine hydrogen-bonding with carboxylic acid. The phenolic part of the acid component is anchored to the water molecule and provides a robust self-assembly. The hydrated cocrystal of sulfamethazine with 3-(4-hydroxyphenyl)propanoic acid (2:2 cocrystal) has two independent molecules of sulfamethazine, one in amidine form and the other in imidine form. It has two neutral carboxylic acids anchored through complementary hydrogen bonds and also has two water molecules of crystallization. The cocrystal of sulfamethazine with 4-(phenyl)phenylcarboxylic acid is also a 2:2 cocrystal. It is a di-hydrate, which has a neutral and protonated form of sulfamethazine. The neutral form is hydrogen-bonded to a neutral carboxylic acid, whereas the protonated form is charge-assisted hydrogen-bonded to the corresponding carboxylate anion.

INTRODUCTION
The tautomeric forms of organic compounds are well known to modulate reactivity and physical properties. Amidine−imidine equilibriums in solution have impacts on excited-state proton transfer processes in emission spectroscopy. Amidine−imidine equilibrium plays an important role in stabilization of a particular tautomer of DNA base-pairs such as in cytosine. Large numbers of organic compounds show amidine−imidine equilibrium. Such equilibriums are studied by various spectroscopic techniques such as nuclear magnetic resonance, infrared spectroscopy, mass spectrometry, and in solid by X-ray crystal structure determination. These equilibriums are stabilized in argon matrix and in practice existence of these forms in solution depend on dielectric and hydrogen bond ability of the solvent. Those factors associated with the solvent help to stabilize any of the forms or allow both to co-exist and the ratio of the forms in solution changes on slight change in conditions. The tautomeric forms are extensively studied by X-ray crystallography. Stabilizations of amidine−imidine forms, a concept of enamine−imine equilibrium, is very common in drugs; either of the forms of a drug bearing such units are accomplished by varying crystallization conditions and by cocrystal formation.

For a solid-state study, crystallizing specifically one form provides an accurate picture of the bond parameters of the...
form and also allows studying their interconversion with isolated cases. The amidine−imidine forms have contributed significantly to the properties such as solubility, bioavailability, and activity of applied pharmaceutical ingredients. Tautomers are also well-known to show polymorphism. Although amidine or imidine forms of a number of drugs are stabilized, there are also certain studies dealing with base-pairs of nucleobases relating the coexistence of the two forms in charge-assisted hydrogen-bonded dimers. The amidine−imidine forms equilibrate through a shift of acidic proton from one site to another site with structural changes to generate two structures of relatively comparable energies. Among them, a good number of examples yield polymorphs. The weak interactions such as anion−π interactions are dependent on the tautomeric form with which the anion can interact. The self-assemblies of multicomponent systems are utilized in modification of fluorescence properties. In acidic condition any of these tautomers gets easily protonated at one of the nitrogen atoms of the two independent sites. Hence, it may be possible to prepare protonated species to coexist in different combinations as illustrated in Figure 1a. As a case study, we have studied here N-substituted pyrimidin-2-amine that may adopt amidine−imidine (analogous of enamine−imine) forms (A and B) and their corresponding mono-protonated forms C and D as shown in Figure 1a. The Cambridge structural database (CSD) search shows that among 232 hits for aminopyrimidine structures, only four examples on coexistence of cation and neutral forms are available. There are also examples of dicationic species of aminopyrimidine. On the other hand, there are 199 hits in CSD for the structures of 2-aminopyridine; there are six examples dealing with neutral and cation forms in the same compound. Recently, we have found that aggregated assemblies of two independent polymorphs can be the third polymorph. As such a process is possible under specific conditions, it should be possible to obtain amidinium−amide, amidinium−imide, imidinium−amide, and imidinium−imide (F-I) forms in cocrystals. There are examples of the amidine and imidine forms stabilized in cocrystals. It has also been shown that sulfamethazine forms a salt or a cocrystal with saccharine on slight variation of crystallization conditions. Another point that enthused us was that, specific cocrystals exist as assembly

![Figure 1.](https://example.com/figure1.png)

(a) Amidine−imidine equilibrium and different combinations of neutral and monocationic forms of N-aryl- or alkyl-pyrimidin-2-amine. (b) Structure of sulfamethazine and the partner acids used as cocrystal partner in this study.
of symmetry nonequivalent pairs. The sulfamethazine (abbreviated as SM) is an N-functionalized pyrimidin-2-amine derivative having a structure shown in Figure 1a. It forms various cocrystals with different carboxylic acids in the amine or imine form. Depending on the acid–base properties certain nitrogen-containing sulf-a-drugs are well known to form a salt or a cocrystal with carboxylic acid. There are 43 crystal structures directly relating sulfamethazine are found in CSD search. Out of these there is a structure of a 2:1 cocrystal of sulfamethazine with theophylline that has coexistence of amidine and imidine tautomers together in its structure; this was referred to as a hydrogen-shift isomerization. Thus, we have chosen sulfamethazine to study cocrystals with different acid partners of which crystal structures were not determined earlier and we also could get suitable di·acid partners of which crystal structures were not determined (abbreviated as amine derivative having a structure shown in Figure 1b. It was referred to as a hydrogen-shift isomerization. Thus, we unravel the form E where the two forms, this study are listed in Figure 1b. From the structural analyses to carry out the structural study. The partner acids studied in earlier and we also could get suitable di·acid partners of which crystal structures were not determined.

Among the five structures of cocrystals examined in this study, the structures of two cocrystals are conventional. Each has a 1:1 molar ratio of SM and carboxylic acid. These two cocrystals are with 2-mercaptopenycarboxylic acid and 4-(4-hydroxy phenylazo)phenylcarboxylic acid. The cocrystal with 2,6-pyridinedicarboxylic acid has also methanol as another counterpart where SM/acid/methanol are in a 1:1:1 molar ratio. However, the other cocrystals with 3-(4-hydroxyphenyl)-propanoic acid or 4-(phenyl)phenylcarboxylic acid are exceptions. They have SM to carboxylic acid in a 2:2 molar ratio and each is a hydrated cocrystal.

**SM-TSCA.** The self-assembly of the cocrystal of 2-mercaptopenycarboxylic acid with SM (SM-TSCA) has the amidine form of SM linked to the carboxylic acid functional group through complementary hydrogen-bonded units with R32(8) graph-set notation. The assembly is formed by O3–H3A–N3 and N2–H2A···O4 hydrogen bonds. The S–H bond of the TSCA is not involved in the intramolecular hydrogen bond, which is utilized to hold a neighbor SM molecule though S–H···π interactions (d(S···π) 3.232 Å). The S–H···π interactions are observed with negatively charged electronically tunable aromatic π-face. The reported structures of a cocrystal of SM-3-hydroxy-2-naphthoic acid as well as that of SM-1-hydroxy-2-naphthoic acid are guided by two independently distinguishable type synthons with R32(8) graph-set notations. In the cocrystal SM-3-hydroxy-2-naphthoic acid the SM molecule exists in amidine form, whereas in the case of the self-assembly of the SM-1-hydroxy-2-naphthoic acid, the SM molecule is in amidine form. In the present case of the SM-TSCA cocrystal, the amidine form is observed. The SM molecules are arranged as a cyclic assembly as illustrated in Figure 2b and are guided by N–H···O interactions between the –SO2− and NH2– group of the neighboring molecules also through C–H···π interactions one each from C–H bonds of methyl-groups with the π-cloud of the pyrimidine ring (d(CH···π(centroid)) 3.014 Å). The cyclic assemblies are formed because of the change in shape of the SM molecules, which adopt a propeller shape in lieu of the regularly observed V-shape geometry.

**SM-PDC-MeOH.** The cocrystals of dicarboxylic acid such as SM-fumaric acid were earlier observed in a 2:1 molar ratio. When we studied the cocrystal of the 2,6-pyridinedicarboxylic acid abbreviated as SM-PDC-MeOH we found out that the cocrystal crystallized from a methanol solution of SM and PDC in a 1:1 molar ratio. The cocrystal has a molecule of SM, a PDC, and a methanol molecule as constituents. The nitrogen atom of the PDC does not form a hydrogen bond with SM directly; but the nitrogen atom is involved in a hydrogen bond with a methanol molecule. The methanol molecule serves as a

**RESULTS AND DISCUSSION**

Among the five structures of cocrystals examined in this study, the structures of two cocrystals are conventional. Each has a 1:1 molar ratio of SM and carboxylic acid. These two cocrystals are with 2-mercaptopenycarboxylic acid and 4-(4-hydroxy phenylazo)phenylcarboxylic acid. The cocrystal with 2,6-pyridinedicarboxylic acid has also methanol as another

![Figure 2](https://example.com/figure2.png)

**Figure 2.** (a) Illustrations of hydrogen bonds and the S–H···π interaction in the cocrystal SM-TSCA; (b) robust cyclic assembly formed by self-interactions among SM molecules in SM-TSCA.
hydrogen bond donor and also as a hydrogen bond acceptor to interact with the PDC. The nitrogen atom of the pyridine dicarboxylic acid forms an O–H⋯N hydrogen bond with the OH of the methanol and one of the C=O of the carboxylic acid also hydrogen bonds with the OH of the methanol molecule to generate bifurcated hydrogen bonds. The oxygen atom of the methanol hydrogen bonds to the −OH group of the other carboxylic acid of the PDC. The facial approach of the SM gets inhibited from one side to form a hydrogen bond with the PDC because of those hydrogen bond schemes. Hence, this is a reason that facilitated the formation of a 1:1 co-crystal in methanol. The oxygen atoms that are exposed outwards on one face of the PDC form hydrogen bonds with the SM molecule through O6–H⋯N3 and N2–H⋯O5 hydrogen bonds. The hydrogen bond donor–acceptor distances depicted in Figure 3 as $d_1$ and $d_2$ and the bond parameters listed in the Supporting Information suggest the synthon to be composed of strong hydrogen bonds. The synthon formed by these interactions is similar to the commonly observed hydrogen bonds between the amidine form of the SM binding to a carboxylic acid. The SM molecule adopts the conventional amidine form. The carboxylic acid group of each PDC having the carboxylic O–H not participating in the hydrogen bond with the methanol molecule anchors an SM molecule through a conventional $R_2^2(8)$ type synthon. The exposed face of the carboxylic acid at the other side is involved in the hydrogen bond with methanol to form weak C8–H8C⋯O3 and C10–H10⋯O4 hydrogen bonded $R_2^2(8)$ synthons. The donor–acceptor distances demarcated as $d_3$ and $d_4$ are marked in
These distances are within the admissible limit to have such weak interactions, and in general C–H···O interactions contribute to stability of noncovalent self-assemblies. Thus, there are two independent $R_2^2(8)$ synthons from the two carboxylic acid groups of the PDC; one is strongly held by moderate hydrogen bonds, whereas the other is by weak hydrogen bond interactions. The prominent hydrogen bonds depicting the self-assembly of the cocrystal is shown in Figure 3. The methanol molecule is held by hydrogen-bonding with two carboxylic acids and is positioned unsymmetrically, forming $R_2^3(9)$ and $R_2^2(7)$ synthons. The $R_2^3(9)$ has involvement of the one of the oxygen atoms of the $-\text{SO}_2-$ group through C20–H···O2 interactions. The PDC molecules provide a hydrogen-bonded bridge to hold two molecules of SM at two sides as depicted in Figure 3. These bridging interactions of the PDC provide a one-dimensional chain-like structure. Together with these interactions one of the N–H of the $-\text{NH}_2-$ group of the phenylamine part form hydrogen bonds with the oxygen atom of the $-\text{SO}_2-$ group of another SM molecule located in the near vicinity. This provides extended hydrogen-bonded self-assembly.

**SM–ABA·H$_2$O.** There are examples in literature of SM cocrystals with aromatic carboxylic acid bearing the hydroxy or the amino group at the para-position of the ring. It was found that in the cocrystals, SM-4-hydroxybenzoic acid as well as in the SM-4-aminobenzoic acid a conventional V-shape structure of SM was not observed but a propeller shape was observed. Here, we have studied the cocrystal of SM with 4-(4-hydroxyphenylazo)phenylcarboxylic acid (ABA) which has a hydroxy-aromatic ring linked to a carboxylic acid unit though an intervening azo-group. The cocrystal of SM with ABA is a hydrated 1:1 cocrystal having a composition SM·ABA·H$_2$O.

The amidine form of SM in the propeller shape is observed in this cocrystal; the SM molecule anchors the carboxylic acid functional group in a routine manner through formation of $R_2^2(8)$ synthony, which comprises N2–H···O4 [$D_{d-a} = 2.802(3)$ Å] and O5–H···N3 [$D_{d-a} = 2.685(3)$ Å] moderate hydrogen bonds (refer to Supporting Information Table S1). In this example, the functional groups attached to the N–N group are in trans-disposition. The water molecules act as linkers between the oxygen (O2) atom of the $-\text{SO}_2-$ group and the oxygen atom (O3) of the hydroxy-group of the neighboring molecules. The hydrogen atom (H1B) of the NH$_1-$ group is hydrogen-bonded to the oxygen atom (O1) of the $-\text{SO}_2-$ group of independent molecules (Figure 4). These interactions provide robust hydrogen-bonded assembly with spiral arrangements.

**SMamidine·SMimidine·2(PA)·2H$_2$O.** The cocrystal of a hydroxyphenyl unit containing carboxylic acid with SM, namely of 3-(4-hydroxyphenyl)propanoic acid (PA), was also studied. We found that this cocrystal has a completely different composition from the other cocrystals studied here. It is a cocrystal where there are two SM molecules per cocrystal; the two constituents of SM are structurally different; one is in amidine and the other in imidine form (abbreviated as SM$_{\text{amidine}}$ and SM$_{\text{imidine}}$, respectively). Along with these there are two neutral PA molecules as partner molecules. There are...
also two molecules of water in each cocrystal. In general, the
cocrystals of SM have the amidine or the imidine form of SM.
One of these two forms occurs in a cocrystal when there is a
small energy difference between the two cocrystal forms.37 In
the present case, having both these forms together, each of
which interacts with partner molecules in independent
fashions, makes it an unusual example. Though there was an
example in the literature of the amidine–imidine form in a
cocrystal,62,63 in that example the amidine and imidine forms
occurred as dimers, which is not the case in the present
element. The amidine portion of the cocrystal has a
conventional hydrogen-bonded R22(8) synthon (Figure 5).
The imidine form of the SM molecule loses the aromaticity
and the hydrogen ion migrates from the N–H to one ring
nitrogen, which creates a hydrogen bond donor site at a
position exactly opposite to the amidine form. This change also
provides complementary geometry to form a hydrogen bond
with the carboxylic acid. Accordingly, it forms an R22(8)
hydrogen-bonded cyclic synthon. The differences in the bond
distances in the two synthons are listed in Figure 5a. The
carboxylic acid–amidine hydrogen-bonded heterodimERIC
synthon has d1 = 2.896 Å and d2 = 2.619 Å. However, the
amidine form is of higher symmetry and it has d1 = 2.759 Å, whereas d2 = 2.713 Å. The relatively short hydrogen
bond with a more symmetric structure is suggestive of the sp3-
character of the N–H center of the amidine which makes a
difference to the sp3-nitrogen center of the imidine. In the case of
the acid–amidine synthon, the ring nitrogen atom of SM is
involved in aromaticity and the extended conjugation involving
the SO2 group with this nitrogen atom is lacking. It makes
slightly different environments than the other counterpart.
The lattice water molecule participates in the bifurcated hydrogen-
bonding with this synthon to make another supportive
synthon. This is not case with the acid–imidine synthon
(refer to Figure 5a). The water molecules in the self-assembly
act as fillers and provide extra support to form a tight-packed
structure by maximum utilization of the available hydrogen
bond sites. The water molecules are held between the hydroxy
and the −SO2− groups in different manners because of
the changes in the hydrogen-bonding schemes originating from
amidine–imidine forms. A portion of the imidine–acid
synthon is connected to the −SO2− group where there is an
extended conjugation. The synthon provides complementary
geometry for having the O11−H11B···O4 hydrogen bond.
Thus, the supportive hydrogen bond schemes associated across
the two R22(8) cyclic units of amidine–acid, amidine–acid
synthons are different and contribute to stabilize a more
symmetric or less symmetric synthon. The prominent weak
interactions distinguishing the two different synthons within
the self-assembly of the cocrystal are shown in Figure 5a.
Furthermore, the amidine and imidine SM molecules are
positioned in a very orderly manner in alternative positions;
each is linked through N1–H1A···O4 and N5–H5A···O1
interactions as depicted in Figure 5b. The hydrogen bond
parameters are included in the Supporting Information Table S1.
The chains formed are aligned in a parallel manner to
provide a Herringbone structure. There are also C–H···π
interactions, highlighted in Figure 5b. These interactions are
suggested on the basis of the observed distances of the C–H
groups projecting perpendicular to the aromatic rings.69 The
C–H···π interactions contribute to the stability of the assembly
and help the rings participating in such interactions to remain
in a near perpendicular manner to each other. The amidine
rings and the 4-hydroxyphenyl rings in the lattice are parallel
and the centroid to centroid distance is 3.875 Å. This distance
is larger than the generally required 3.5 Å distance to have
highly favorable π···π interaction,70 but the parallel stacks
between the rings of which one is electron rich and other is
electron-deficient contribute to the self-assembly in a
constructive manner.

(SM)(HSM)·(HBPA)(BPA)·2H2O. On the other hand, the
cocrystal of 4-(phenyl)phenylcarboxylic acid with SM has
provided a new insight. It has one neutral, one protonated SM
molecule (abbreviated as HSM) along with a neutral HBPA
molecule and a BPA anion. The structure of the cocrystal
(SM)(HSM)·(HBPA)(BPA)·2H2O is shown in Figure 6a.
Depending on the pKa a large number of amidine-based
compounds form cocrystals or salts. In those cases, acid–base
properties with narrow pKa differences have a tendency to form
either of the forms.30 However, the cocrystal with 4-(phenyl)
phenylcarboxylic acid has both the forms, namely neutral and protonated forms of SM in the same cocrystal. In
the self-assembly, a grid-like architecture is formed by the SM
and HSM molecules are positioned next to each other. The
neutral and protonated forms are in amidine form and each has
a propeller shape. They are linked to each other through weak
N–H(phenylamine)···O(SO2) interactions in head-to-head arrange-
ments so that pyrimidine parts are almost vertically held on the
chain. Another chain of same kind assemblies provide hydrogen
bonded grid-like assembly in which the voids are occupied by
the BPA molecules. The aromatic ring of the BPA and the
pyrimidine rings of SM are parallel to each other. The phenyl
ring at the para-position of the phenylcarboxylate anion is
involved in π·· interactions with the amidine ring of the
neutral form. The π·· centroid distance in this case is 3.658 Å. The
two phenyl rings of the HBPA molecule in neutral form are in
one plane, whereas in the case of the anion these are not in one plane. The dihedral angle between the planes of the two phenyl

Figure 7. Hirshfeld surface analyses showing the hydrogen bonds of the carboxylic acids and carboxylates (a) (SMamidine)(SMimidine)·2(PA)·2H2O and (b) SM-HSM-HBPA-BPA·2H2O.
The protonated form provides two hydrogen bond donors forming SM molecule is protonated on the pyrimidine ring. The parallel to the pyrimidine ring of the neutral form has a symmetric synthon as the dicarboxylate anion is charge-assisted hydrogen bonds. Hence, the proton-transfer has caused the ionic forms not only to get involved in charge-assisted hydrogen bonds. A comparison of the two R2\textsuperscript{1}(8) synthons shows that the neutral form has d\textsubscript{1} and d\textsubscript{2} of 2.661 and 2.805 Å, respectively, whereas the ionic form has d\textsubscript{1} and d\textsubscript{2} of 2.758 and 2.709 Å, respectively. The latter has a symmetric synthon as the dicarboxylate anion is delocalized where the two C–O environments are similar. The C–O bonds of the carboxylate have partial double-bond character.

#### STRUCTURAL COMPARISONS

The Hirshfeld surface analysis of each cocrystal is carried out using the corresponding crystallographic information file. The

![Figure 8](image-url)

**Figure 8.** Relative differences in the theoretical gas-phase energies of different forms of SM calculated by DFT based on the B3LYP functional using 6-311G**+**(2df,2p) as the basis set.

analyses are suggestive of the fact that the O–H interactions are predominant in each case and their contribution varied from ~23 to ~29%. The relative contributions of the different hydrogen bonds are listed in the Supporting Information Table S3. The hydrogen bond interactions of the carboxylic acid/carboxylate ion with SM/HSM are revealed from the surface analysis in each case. As a representative case the surface analyses establishing these features in the 2:2 cocrystals are shown by red marks on the surfaces in Figure 7.

The cationic and neutral forms of amino-pyridines are observed generally in the salts with large anions such as polyoxometalate anions or as ionic cococrystals. However, in the present case it has been possible by utilization of the extra supramolecular features on the amidine scaffold of the SM molecule to stabilize pairs with and without charge-assisted hydrogen bonds in the same compound. The above discussions have clearly established the coexistence of two or more forms in the same cocrystal. In earlier examples, two symmetry nonequivalent molecules of SM and two carboxylic acid molecules were observed in the asymmetric unit of the cocrystal of SM with 1-hydroxy-2-naphthoic acid. Narrow energy differences between the different cococrystals having different tautomeric forms are a reason to observe a particular form under a suitable condition. We have calculated independently the energy of the neutral forms of the sulfamethazine and two possible protonated states of SM; the results are shown in Figure 8. It is found that the amidine form is stable and the energy difference between the amidine and imidine in the neutral form is 48.40 kJ/mol. The difference in the protonation of amidine at the ring nitrogen and exocyclic secondary amine is also calculated and it is found that the ring protonation is favorable by 41.05 kJ/mol. An acid with moderate acidity may not easily protonate SM. Hence, in such a case other factors come into play; for example the cocrystal of the 4-(phenyl)phenylcarboxylic acid forms ionic cococrystals having a charge-assisted hydrogen bond to maximize the charge-transfer interactions between the rings.

To demonstrate the existence of the different forms in the unit cell, such as the combinations of the tautomeric forms or combination of protonated and neutral forms of SM in these cococrystals, a comparison of the C=N and C=N bond distances of the amidine and imidine and protonated rings are compiled in Table 1. The C=N bond distances of different forms available from selected representative references are also compared in Table 1 with them to show the agreement of our assignments. The bond distances of the C=N bond in the ring of the neutral amidine form are between 1.317 and 1.354 Å. These values of bond distances fall in between the conventional C=N bond and C=N bond distance of 1.47 and 1.25 Å, respectively. The difference in the two C=N bonds of the rings in each case is slightly different. The bond observed in the exocyclic C=N bond distance of the amidine form varies between 1.366 and 1.401 Å. This variation is comparatively large and is attributed to the participation of the electrons on the nitrogen atom in conjugation with the aromatic ring. The efficiency of the partner acid to participate in complementary hydrogen bonds decides the faith of formation amidine–acid or imidine–acid synthon. There are distinct bond distances, by which the amidine and imidine forms can be clearly distinguished. The imidine form of (SM\textsubscript{imidine})(SM\textsubscript{imidine})\textsuperscript{+}\textsuperscript{−} 2(PA)\textsubscript{−}2H\textsubscript{2}O has an exocyclic C=N bond distance of 1.348 Å and there are two bond distances for the endocyclic C=N bond (one is 1.338 Å and other is 1.355 Å). These two distances indicate extended conjugation in the imidine form. The protonated and neutral forms also have distinguishable bond distances, for example, the protonation at the ring causes elongation of the one endocyclic C=N bond where the proton is attached. The distances are compared with several other common cococrystals and salts found in literature. We found that our results on different bond parameters in the observations of multiple rings are valid as compared to the others. There is an example of a cocrystal of SM with 1-hydroxy-2-naphthoic acid in which two symmetry non-equivalent cococrystals of SM were observed. In such a case, the bond parameters of the two amidine forms have close similarities (Table 1), but our coexisting amidine and imidine forms have distinguishable bond distances. Several other cococrystals involving purely the neutral form of SM are available in literature.

There is a report of the salt of 2-carboxy-4,6-dinitrophenolic acid with SM; the cationic part of this salt has similar bond parameters as that of the protonated amidine unit observed in the SM of the salt with 4-(phenyl)-phenylcarboxylic acid. The difference in the latter case had
an additional neural SM molecule together with a neutral BPA molecule in the cocrystal. This increases the number of different forms of components within the unit cell, which is an interesting observation.

Once these cocrystals are dissolved in solvents used for NMR study, only the proton signals of the parent components are observed without any significant shift from the original cases. Hence, the forms clearly discernible in solid are not distinguishable in solution. The 1H NMR spectra of the cocrystals have revealed that only the amidine form in each case is seen in their respective solution. Same is the case with the neutral and protonated forms. There is no distinction in solution once the cocrystal (SM)(HSM)·(HBPA)(BPA)·2H2O is dissolved in DMSO-d6 (please refer to the Supporting Information NMR spectra). These indicate that the stable form is observed in solution and the special features seen in the tight-packed structures of solid samples are lost. However, the physical properties of solids are dependent on the solvation and the conformers. In the thermogravimetric study (Supporting Information Figure S16) it was observed that weight loss corresponding to loss of water molecules from the hydrated cocrystals corresponded to the weight of the amount of hydrated water present per mole in the respective cocrystal. Namely, the SM·ABA·H2O, (SMamidine)(SMimidine)·2(PA)·2H2O, and SM·HSM·HBPA·BPA·2H2O lose water molecules at the ranges 91−112 °C (decomposes at >200 °C), 70−95 °C (decomposes at > 150 °C), and 95−115 °C (decomposes at >200 °C), respectively. The SM-PDC-MeOH loses methanol

### Table 1. Comparison of C−N Bond-Distances Observed in the Different Forms of SM Found in Cocrystals and Salts

| Compound                  | Observed forms of the SM | Bonds                  |
|---------------------------|--------------------------|------------------------|
| SM·TSCA                   | Neutral amidine          | C1-N1: 1.367(4)        |
|                           |                          | C1-N2: 1.324(4)        |
|                           |                          | C1-N3: 1.350(4)        |
| SM·PDC·MeOH               | Neutral amidine          | C1-N1: 1.384(6)        |
|                           |                          | C1-N2: 1.337(6)        |
|                           |                          | C1-N3: 1.343(6)        |
| SM·ABA·H2O                | Neutral amidine          | C1-N1: 1.366(4)        |
|                           |                          | C1-N2: 1.330(3)        |
|                           |                          | C1-N3: 1.354(3)        |
| (SMamidine)(SMamidine)·2(PA)·2H2O | Amidine and imidinide  | C1-N1: 1.399(4)        |
|                           |                          | C1-N2: 1.323(4)        |
| (SM)(HSM)(HBPA)(BPA)·2H2O | Neutral amidine and protonated amidine | C1-N1: 1.379(5)        |
|                           |                          | C1-N2: 1.328(5)        |
| SM·1-hydroxy-2-naphtholic acid | Two molecules of | C1-N1: 1.389(2)        |
|                           |                          | C1-N2: 1.332(2)        |
| SM·3-hydroxy-2-naphtholic acid | Neutral amidine | C1-N1: 1.345(2)        |
|                           |                          | C1-N2: 1.357(2)        |
| SM·saccharine             | Neutral amidine          | C1-N1: 1.345(2)        |
|                           |                          | C1-N2: 1.357(2)        |
| HSM·saccharine            | Protonated amidine       | C1-N1: 1.343(2)        |
|                           |                          | C1-N2: 1.352(3)        |
| (SMamidine)(SMamidine)·2(PA)·2H2O | Amidine and imidinide  | C1-N1: 1.401(2)        |
|                           |                          | C1-N2: 1.331(2)        |
| HSM·2-carboxy-4,6-dinitrophenolate | Protonated amidine   | C1-N1: 1.386(3)        |
|                           |                          | C1-N2: 1.356(4)        |
|                           |                          | C1-N3: 1.323(4)        |

### Table 2. Ranges of Bond-Parameters Differentiating Different Forms of SM

| Different forms | Observed ranges of Bond distances (Å) | Bonds |
|-----------------|----------------------------------------|-------|
| N3-C1-N1        | 113.83−115.80                         | C1-N1: 1.366-1.401 |
| N2-C1-N1        | 117.44−120.78                         | C1-N2: 1.317-1.332 |
| N1-C1-N2        | 124.97−128.73                         | C1-N3: 1.328-1.354 |
| C1-N1-S1        | 123.85−127.94                         |       |
| N3-C1-N1        | 120.82−122.09                         | C1-N1: 1.357-1.364 |
| N2-C1-N1        | 114.92−115.85                         | C1-N2: 1.329-1.356 |
| C1-C1-N1        | 122.99−123.34                         | C1-N3: 1.322-1.354 |
| C1-N1-S1        | 122.46−125.84                         |       |
| N3-C1-N1        | 123.19−125.97                         | C1-N1: 1.337-1.348 |
| N2-C1-N1        | 113.18−115.24                         | C1-N2: 1.338-1.367 |
| C1-C1-N1        | 120.52−121.67                         | C1-N3: 1.342-1.355 |
| C1-N1-S1        | 120.13−122.99                         |       |
at 55−70 °C (decomposes at >230 °C), whereas the cocrystal SM·TSCA being anhydrous, it does not show any weight loss before its decomposition above 200 °C. The melting point of cocrystals of sulfamethazine differs from parent SM and varies with partner molecules. The differential scanning calorimetry (DSC) has been extensively used to predict the composition in lower temperature of 73 °C followed by melting at 115 °C, followed by melting at 213 °C.

The sulfamethazine melts at 198 °C. The anhydrous cocystal SM·TSCA melts at 172 °C. The solvated 1:1 cocystal SM·PDC·MeOH shows a broad endothermic peak extending from 60 to 90 °C because of loss of methanol, followed by melting at 214 °C. It also shows another endothermic peak at 223 °C. The SM·ABA·H2O loses water molecules at 106 °C, followed by melting at 213 °C. The (SMimidine)(SMimidine)-2(2:PA)-2H2O loses water at a relatively lower temperature of 73 °C followed by melting at 148 °C. The sulfamethazine and the acid conformers used in this study make a combination of protonated and neutral partner molecules together in a cocrystal with the neutral and anion of the other counterpart. These findings open up avenues for new cocrystals of applied pharmaceutical ingredients by choosing suitable partner molecules.

### EXPERIMENTAL SECTION

The sulfamethazine and the acid conformers used in this study were purchased from Sigma-Aldrich Co. Each cocystal was prepared by dissolving sulfamethazine (278 mg, 1 mmol) in reagent-grade methanol (25 mL) and to it the respective carboxylic acid (1 mmol) was added and stirred so that a clear solution was observed. In each case the reaction mixture was filtered after stirring for half an hour using Whatman filter

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**Table 3. Crystallographic Parameters of Different Cocrystals of SM**

| SM·TSCA | SM·PDC·MeOH | SM·ABA·H2O | (SMimidine)(SMimidine)-2(2:PA)-2H2O | SM·HSM·HBPA·BPA·2H2O |
|---------|-------------|------------|-----------------------------------|----------------------|
| formula | C19H20N4O4S2 | C20H23N5O7S1 | C25H26N6O6S1 | C21H26N4O6S1 | C50H52N8O10S2 |
| CCDC no. | 1903711 | 1903709 | 1903710 | 1903707 | 1903708 |
| mol. wt. | 432.51 | 477.49 | 538.58 | 462.52 | 989.11 |
| space group | P21/c | P21/n | P21/c | P21/c | P21/c |
| α/˚ | 11.002(3) | 8.1221(8) | 9.3634(12) | 13.4476(16) | 18.841(2) |
| β/˚ | 13.517(4) | 22.8639(13) | 29.190(4) | 18.531(2) | 14.3390(7) |
| γ/˚ | 13.733(4) | 13.0456(11) | 9.6803(12) | 18.531(2) | 18.2135(7) |
| density/g cm⁻³ | 1.407 | 1.367 | 1.383 | 1.325 | 1.285 |
| abs. coeff./mm⁻¹ | 0.294 | 0.190 | 0.178 | 0.183 | 0.168 |
| total no. of reflections | 3614 | 4119 | 4587 | 8187 | 9035 |
| reflections, I > 2σ(I) | 2961 | 2542 | 3333 | 5435 | 6054 |
| max. θ/˚ | 25.037 | 25.047 | 25.049 | 25.047 | 25.049 |
| ranges (h, k, l) | -13 ≤ h ≤ 13 | -9 ≤ h ≤ 9 | -11 ≤ h ≤ 11 | -16 ≤ h ≤ 16 | -21 ≤ h ≤ 23 |
| data/restraints/parameters | 36143/284 | 41190/308 | 45873/362 | 81875/620 | 90350/645 |
| GooF | 1.043 | 1.091 | 1.020 | 1.030 | 1.177 |
| R indices [I > 2σ(I)] | 0.0585 | 0.0828 | 0.0523 | 0.0625 | 0.0775 |
| wR² [I > 2σ(I)] | 0.1708 | 0.1258 | 0.1498 | 0.1599 | 0.1482 |
| R indices (all data) | 0.0864 | 0.1294 | 0.0728 | 0.1004 | 0.1102 |
| wR² (all data) | 0.1816 | 0.1410 | 0.1664 | 0.1904 | 0.1633 |

In conclusion, we have divulged a new rare example of having two tautomeric forms, namely amidine and imidine forms of the same compound together in a cocrystal and made a comparison of the prominent bond parameters contributing to the neutral amidine, protonated amidine, neutral imidine forms of SM found in the cocrystals and salts. The ranges of the prominent bond parameters from the forms differentiating each form presented here and the reported ones from the CSD that distinguish them are listed in Table 2. Though there was an example of a 1:2 cocrystal of theophylline with SM, possessing amidine/imidine tautomers together in the cocrystal, we have two pairs of amide form as well as imidine form hydrogen-bonding independently with two molecules of 3-(4-hydroxyphenyl)propionic acid (2:2 molar ratio); a unique example of the cocrystal of SM that has a combination of protonated and neutral partner molecules together in a cocrystal with the neutral and anion of the other counterpart. These findings open up avenues for new cocrystals of applied pharmaceutical ingredients by choosing suitable partner molecules.
paper to remove residue (if any). The transparent solution thus obtained in each case was kept independently undisturbed inside fume-hood to slowly evaporate at 25 °C. The crystals were allowed to form in the solution in an undisturbed manner until the volume of the solution became 3 mL (approximately) in each case, which was completed in 6–7 days. The yields of crystals are listed in the Supporting Information. The complete removal of the solvent did not increase the yield of the highly pure crystals; hence, optimum residual solvent in each solution was required to get highly pure and suitably diffracting crystals.

Physical Measurements. Infrared spectra of the solid samples were recorded on a PerkinElmer Spectrum-One FT-IR spectrophotometer in the region 4000–400 cm⁻¹ by making KBr pellets. ¹H NMR spectra of sulfamethazine and the cocrys- tals were recorded on a Bruker Ascend-600 MHz NMR spectrometer using TMS as internal standard. DSC and thermogravimetry studies were performed using a thermal analyzer SDTQ600 simultaneous DTA/TG system under nitrogen with a heating rate of 5 °C/min. Powder X-ray diffraction patterns were recorded using a Bruker powder X-ray diffractometer D2-phase. Hirshfeld analyses are done by using Crystal Explorer 3.1 software. DFT calculations were done by using Gaussian 09 software. Optimizations were done by DFT using B3LYP functional with 6-311G**(2df,2p) as the basis set.

Crystallographic Study. The X-ray single-crystal diffraction data for the SM-PDC-MeOH and (SM)(HSM)-(HBPA)-(BPA)-2H2O were collected by an Oxford SuperNova diffractometer and the data refinement and cell reductions were carried out by CrysAlisPro. The diffraction data of the other cocrys- tals were collected at room temperature with Mo Kα radiation (λ = 0.71073 Å) on a Bruker Nonius SMART APEX CCD. The diffractometer has a graphite monochroma- tor and an Apex CCD camera. SMART software was used for data collection and also for indexing the reflections and determining the unit cell parameters. Data reduction and cell refinement were performed using SAINT and XPREP software. Structures were solved by direct methods using SHELXS-14 and were refined by full-matrix least-squares on F² using SHELXL-14. All nonhydrogen atoms were refined in anisotropic approximation against P² of all reflections. Hydrogen atoms were placed at their geometric positions and either set to be “fixed” or “riding and refined” in the isotropic approximation. The crystallographic parameters are listed in Table 3.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01437.

¹H NMR, PXRD, FT-IR spectra, DSC, TG, Hirshfeld analysis, hydrogen bond parameters, and XYZ coordinates of the optimized structure done by DFT calculation (PDF)

Crystallographic data of SM (CIF)

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Notes

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