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The Salt−Cocrystal Continuum: The Influence of Crystal Structure on Ionization State

Scott L. Childs, G. Patrick Stahly, and Aeri Park*

SSCI, Inc., an Aptuit company, 3065 Kent Avenue, West Lafayette, Indiana 47906

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Abstract: Salts and cocrystals are multicomponent crystals that can be distinguished by the location of the proton between an acid and a base. At the salt end of the spectrum proton transfer is complete, and on the opposite end proton transfer is absent in cocrystals. However, for acid−base complexes with similar pK_a values, the extent of proton transfer in the solid state is not predictable and a continuum exists between the two extremes. For these systems, both the ΔpK_a value (pK_a of base − pK_a of acid) and the crystalline environment determine the extent of proton transfer. A total of 20 complexes containing theophylline and guest molecules with ΔpK_a values less than 3 have been prepared, resulting in 13 cocrystals, five salts, and two complexes with mixed ionization states based on IR spectroscopy and single-crystal diffraction data. We propose modifications to the ΔpK_a rule for selecting salt screen counterions that focus on the discovery of solid forms with useful physical properties rather than an arbitrary cutoff value for ΔpK_a.

Keywords: Salt; cocrystal; pK_a, proton transfer; molecular complex; pharmaceutical

Introduction

Pharmaceutical scientists constantly strive to improve physical properties of active pharmaceutical ingredients (APIs) such as crystallinity, solubility, hygroscopicity, stability, particle size, flow, filterability, density, and taste.[1] The desired improvements can be often achieved by making a different solid form of an API. When crystalline solid forms are desired, research efforts have focused on identifying polymorphs, hydrates, solvates, salts, and, more recently, cocrystals of an API.

Cocrystals have been known at least since the late 19th century,[2] but have only recently gained attention as an additional tool in the pharmaceutical field.[3] There is considerable debate surrounding the definition of the term "cocrystal". Indeed it seems that the community at large cannot even agree on whether it is "cocrystal" or "co-crystal",[4] let alone exactly what constitutes a cocrystal and what does not. Most agree with the general statement, "a cocrystal is a crystalline solid containing multiple components." The controversy involves how to define what a

* Corresponding author. Mailing address: SSCI, Inc., 3065 Kent Avenue, West Lafayette, IN 47906. Fax: 765-463-4722. Tel: 765-463-0427. E-mail: aeri.park@aptuit.com.

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"component" is and what to do when the category of "multicomponent crystals" overlaps with historically entrenched terms such as solvate and hydrate. In the context of this article it is important to understand that we believe that salts and cocrystals can both be described as multicomponent crystals[5] because of the smooth transition that connects these two categories. This does not suggest that a salt is a cocrystal, but rather that salts and cocrystals are both multicomponent crystals. Distinctions between salts and cocrystals can be made based on whether a proton transfer has occurred from an acid to a base.[6] Multicomponent crystals are, in our view, composed of two or more components associated through intermolecular interactions where a component is an atom, ion, or molecule. However, there are numerous molecular complexes where the above definitions of salts and cocrystals do not clearly apply.

It is generally accepted that reaction of an acid with a base will be expected to form a salt if the ΔpK_a ($\Delta pK_a = pK_a$(base) $- pK_a$(acid)) is greater than 2 or 3.[7] For those engaged in preparation of salts to improve properties of APIs, this ΔpK_a criterion is often viewed as essential for the selection of appropriate counterions in a salt selection. Although in general a larger ΔpK_a (greater than 3) will result in salt formation and, as Nangia[7d] noted, a smaller ΔpK_a (less than 0) will almost exclusively result in cocrystal formation, that parameter is inappropriate for accurately predicting salt formation in the solid state when ΔpK_a is between 0 and 3.

The majority of crystalline acid−base complexes have a ΔpK_a value of less than 1 or greater than 3 and with very few exceptions will fall into either the cocrystal or salt categories. It is the relatively narrow region at the interface of salts and cocrystals that is the subject of this research.

Experimental Section

Reagents. All reagents and solvents were purchased from Aldrich Chemical and used as received.

X-ray Powder Diffraction (XRPD). X-ray powder diffraction (XRPD) analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer or Inel XRG-3000 diffractometer. The Shimadzu XRD-6000 diffractometer was equipped with a long fine focus X-ray tube using Cu Kα radiation. The tube voltage and amperage were set to 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1°, and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A $\theta-2\theta$ continuous scan at 3 deg/min (0.4 s/0.02° step) from 2.5° to 40° 2θ was used. The Inel XRG-3000 diffractometer was equipped with a CPS (curved position sensitive) detector with a 2θ range of 120°. Real time data were collected using Cu Kα radiation at a resolution of 0.03° 2θ. The tube voltage and amperage were set to 40 kV and 30 mA, respectively. The monochromator slit was set at 5 mm by 160 μm. The pattern was displayed from 2.5° to 40° 2θ. Samples were prepared for analysis by packing them into thin-walled glass capillaries. Each capillary was mounted onto a goniometer head that was motorized to permit spinning of the capillary during data acquisition. The samples were commonly analyzed for 1 min. Both instruments were calibrated daily using a silicon reference standard.

Single-Crystal X-ray Diffraction. Suitable crystals of each solid form were coated with Paratone N oil, suspended in a small fiber loop, and placed in a cooled nitrogen gas stream at 173 K on a Bruker D8 APEX II CCD sealed tube diffractometer with graphite monochromated Cu Kα (1.541 78 Å) or a Bruker D8 Smart 2K CCD with Mo (0.710 73 Å) radiation. Data were measured using a series of combinations of ϕ and ω scans with 10 to 30 s frame exposures and 0.5° frame widths. Data collection, indexing, and initial cell refinements were all carried out using APEX II[8] software. Frame integration and final cell refinements were done using SAINT[9] software. The structures were solved using direct methods and difference Fourier techniques (SHELXTL, V6.12).[10] Scattering factors and anomalous dispersion corrections are taken from the International Tables for X-ray Crystallography.[11] Structure solution, refinement, and generation of publication materials were performed using SHELXTL, V6.12 software. Additional details of data collection and structure refinement are given in Table 4.

Infrared (IR) Spectroscopy. IR spectra were acquired on a Magna-IR 860 Fourier transform infrared (FT-IR) spectrophotometer (Thermo Nicolet) equipped with an Ever-Glo mid/far-IR source, an extended range potassium bromide (KBr) beamsplitter, and a deuterated triglycine sulfate (DTGS) detector. An attenuated total reflectance (ATR)

(4) We use "cocrystal" because we believe that it is the most grammatically correct term according to the rules of English usage. For instance, see: Wilson, K. G. *The Columbia Guide to Standard American English*; MJF Books: New York, 1993; p 99.

(5) Further discussion on the definitions of salts and cocrystals are detailed in the following publication: Stahly, G. P. Diversity in Single-Component and Multiple-Component Crystals. The Search for and Prevalence of Polymorphs and Cocrystals. *Cryst. Growth Des.*, in press.

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accessory (Thunderdome, Thermo Spectra-Tech), with a germanium (Ge) crystal, was used for data acquisition. Generally, the spectra represent 256 co-added scans collected at a spectral resolution of 4 cm^{-1}. A background data set was acquired with a clean Ge crystal. Log $1/R$ (R = reflectance) spectra were acquired by taking a ratio of these two data sets against each other. Wavelength calibration was performed using polystyrene.

Solution ^{1}H NMR. Solution ^{1}H NMR spectra were acquired at ambient temperature on a Varian ^{UNITY}INOVA-400 spectrometer (^{1}H Larmor frequency = 399.800 MHz). The samples were dissolved in NMR-grade DMSO-d_6 containing 0.03% TMS. Each ^{1}H NMR spectrum represents 40 co-added transients collected with a 8.2-μs pulse and a relaxation delay time of 5 s. The free induction decay (FID) was exponentially multiplied with a 0.2 Hz Lorentzian line broadening factor to improve the signal-to-noise ratio.

pK_a Calculation. All calculated pK_a values were calculated using ACD/pK_a DB version 7.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada. The values were rounded to the nearest 1/10.

Preparation of Theophylline (2) Complexes. Crystals precipitated from solutions were isolated by gravity or vacuum filtration. Solids were analyzed by XRPD, IR spectroscopy, and in some cases proton NMR spectroscopy in DMSO-d_6 to confirm the molar ratio of **2** and guest.

The complexes with carboxylic acids as guests were prepared by dissolving the target stoichiometric amounts of **2** and guests (1:1 molar ratio except for glycolic and chloroacetic acids where excess amounts of guests were used) in appropriate solvents assisted by heating. The following solvents were used: **2**:salicylic acid (water with small amount of methanol), **2**:benzoic acid (3:1 chloroform:ethanol), **2**:5-chlorosalicylic acid (1:1 ethanol:water), **2**:gentisic acid (5:1 water:ethanol), **2**:4-hydroxybenzoic acid (4:1 water:ethanol), **2**:2,4-dihydroxybenzoic acid (1:1 ethanol:chloroform), **2**:1-hydroxy-2-naphthoic acid (acetonitrile), **2**:sorbic acid (1:1 ethanol:water), **2**:glycolic acid (water), **2**:malonic acid (3:1 chloroform:ethanol), **2**:chloroacetic acid (1:2 water:methanol). The clear solutions were allowed to cool to ambient temperature, and solvents were allowed to evaporate slowly (with partial covering) at ambient conditions.

The complexes with primary amines as guests were prepared by dissolving the **2** and excess amount guests in ethanol assisted by heating, followed by adding an equal volume of chloroform. Water was added where hydrates were desired such as **2**:ethylenediamine hydrate and **2**:1,7-heptanediamine hydrate. Hexanes were added to the clear solutions to precipitate solids (sometimes aided by sonication). The anhydrous form of **2**:1,7-heptanediamine was also obtained by grinding the 2:1 molar mixture.

The complex of **2**:piperazine was prepared by dissolving 2:1 molar amounts of **2**:piperazine in 20:1 acetone:water assisted by heating, followed by adding equal volume of chloroform. The clear solutions were allowed to cool to ambient temperature, and solvents were allowed to evaporate slowly (with partial covering) at ambient conditions.

Preparation of 1:1 Niflumic Acid:Maleic Acid Salt. Niflumic acid (28.2 mg) and 11.5 mg of maleic acid were dissolved in 2.5 mL of acetonitrile in a 4 mL vial with heating. The suspension was stirred and warmed with a commercial heat gun on low power until the solids were dissolved. The solution was allowed to cool to room temperature. Slow evaporation of the solution resulted in formation of solids. The solid product was isolated by filtration and air-dried.

Results and Discussion

It is desirable to label and classify crystalline solid forms in order to characterize them and make comparisons; however, in practice this can become problematic because researchers do not always agree on what does or does not belong in a particular category or what the definition of each category is. An attempt was made to address some of this controversy in a recent perspective article.[5] In general, we believe that molecular crystals can be classified broadly into single-component and multiple-component crystals. Multicomponent crystals can be further separated into salts and cocrystals. We advocate that both salts and cocrystals are multicomponent crystals because a continuum exists linking cocrystals and salts based on the extent of proton transfer between the components.

If a solution containing an organic acid and an organic base deposits a crystalline solid containing both components, will that solid be a salt? The current way of thinking is to determine which species the proton is attached to. If the proton resides on the base, then proton transfer has occurred and the crystalline acid−base complex is a salt. If proton transfer has not occurred and the proton remains on the acid, then it is a cocrystal.

The propensity of an acid to give up a proton is represented by its pK_a, the negative logarithm of the dissociation constant. Traditionally, a ΔpK_a value of 2 or 3 is used for selecting counterions for salt preparations.[7] It must be remembered that pK_a relates to equilibrium behavior in aqueous solution and that measured pK_a values will vary depending on measurement technique, solvent, temperature, and other factors. The extent to which proton transfer occurs depends on the relation of the pK_a values of the reacting acid and base, as well as the magnitude of their difference. The effect of the magnitude of pK_a separation on proton transfer can be determined by subtracting the pK_a value of the acid from the pK_a value of the base to give an equilibrium constant. An illustration of these principals is shown below for acetic acid and the bases methylamine and pyridine.

$$CH_3CO_2H \rightarrow CH_3CO_2^- + H^+ \qquad pK_a = 4.76$$

$$\text{pyridineH}^+ \rightarrow \text{pyridine} + H^+ \qquad pK_a = 5.14$$

$$CH_3NH_3^+ \rightarrow CH_3NH_2 + H^+ \qquad pK_a = 10.62$$

For the reaction CH_3CO_2H + pyridine → $CH_3CO_2^-$ + pyridineH$^+$,

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$$K_{eq} = [CH_3CO_2^-][\text{pyridineH}^+]/[CH_3CO_2H][\text{pyridine}] = 10^{5.14-4.76} = 10^{0.38} \approx 2$$

For the reaction $CH_3CO_2H + CH_3NH_2 \rightarrow CH_3CO_2^- + CH_3NH_3^+$,

$$K_{eq} = [CH_3CO_2^-][CH_3NH_3^+]/[CH_3CO_2H][CH_3NH_2] = 10^{10.62-4.76} = 10^{5.86} \approx 7 \times 10^5$$

The absolute pK_a value of the separation between acetic acid and pyridine is 0.38, and on mixing equimolar quantities in water the concentration of the ionized species will be about 2 times greater than the concentration of the un-ionized species. The absolute pK_a value of the separation between acetic acid and methylamine is 5.86, and on mixing equimolar amounts in water the concentration of the ionized species will be about 7×10^5 times greater than the concentration of the un-ionized species.

What would happen if the pK_a value of a base is less than that of the acid giving the ΔpK_a a negative value? For an example, 2-aminopyrimidine (**1**, Figure 1) and 4-aminobenzoic acid form a 1:1 complex, and the calculated pK_a values are shown below:

$$\mathbf{1}H^+ \rightarrow \mathbf{1} + H^+ \qquad pK_a = 3.86$$

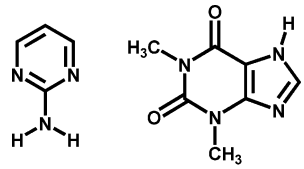
$$\text{4-aminobenzoic acid} \rightarrow \text{4-aminobenzoate}^- + H^+ \qquad pK_a = 4.86$$

For the reaction 4-aminobenzoic acid + **1** → 4-aminobenzoate$^-$ + **1**H$^+$,

$$K_{eq} = [\text{4-aminobenzoate}^-][\mathbf{1}H^+]/[\text{4-aminobenzoic acid}][\mathbf{1}] = 10^{3.86-4.86} = 10^{-1.0} \approx 0.1$$

Therefore, the concentration of un-ionized species will be 10 times greater than the concentration of ionized species in an aqueous solution containing equimolar amounts of **1** and 4-aminobenzoic acid. This equilibrium favors the non-ionized species, and for complexes with negative ΔpK_a values the acid−base interaction in the solid state is almost always non-ionized.

pK_a values describe equilibrium phenomena in solution and are not meant to be applied to the solid state. The situation is in some ways analgous to the use of van der Waals radii in characterizing crystal structures. These values were intended to reproduce volumes and not contact distances in crystals,[12] but despite the misapplication of the van der Waals radii, their pervasive use has made them a well-known and useful concept. In this case, pK_a values are also being used to characterize a system to which they do not apply, but despite the problems associated with using pK_a values to predict the ionization state in crystals, it remains a useful and accessible method that is consistent with the cutoff values we have suggested.



1 **2**

Figure 1. Molecular structures of 2-aminopyrimidine (**1**) and theophylline (**2**).

In the solid state, the extent of proton transfer has been determined from single-crystal X-ray (or neutron) diffraction analysis by evaluating (1) proton location[13] and/or (2) bond lengths of atoms involved, for example, C−O distances of carboxyl groups or phenolic alcohol groups,[14] as well as (3) bond angles.[15] The evaluation can be also carried out by spectroscopic analysis using techniques such as IR spectroscopy to observe O−H, N−H, and COOH signals[7a,14b,16] and

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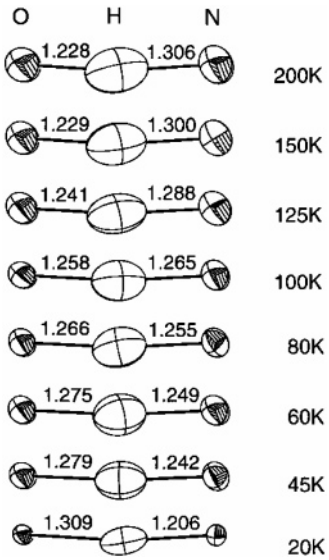

Figure 2. The hydrogen location in a pentachlorophenol:4-methylpyridine complex measured by neutron diffraction at various temperatures. Reproduced with permission from ref 18. Copyright 1893 Chemical Society, London.

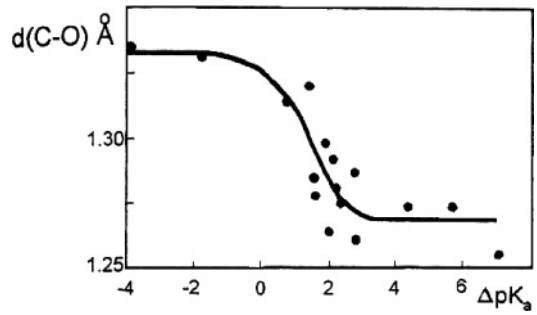

Figure 3. The correlation between the C−O bond length and ΔpK_a values for molecular complexes of phenols. Shorter C−O bond lengths, *d*(C−O), at larger ΔpK_a values indicate salt formation while longer C−O distances at small or negative ΔpK_a values indicate cocrystal formation. Reproduced with permission from ref 14a. Copyright 1997 Elsevier.

IR peak shifts due to hydrogen bonding,[7a,16a,h−j] and solid-state NMR spectroscopy to observe carbon, nitrogen, and phosphorus chemical shifts.[16f,g,17]

When the proton location is ambiguous, neither the salt nor cocrystal label can be applied to accurately describe such a structure. Disorder can lead to observation of multiple protonation states with partial occupancy or the proton location can be described as being "shared" if it is not clearly covalently bonded to either the acid or the base. In fact, when considering the location of the proton in such complexes, a continuum exists between the two extremes of salt and cocrystal. A recent study[17] identified a carboxylic acid−pyridine interaction in which the authors describe the proton location as "shared" based on single-crystal X-ray diffraction and ^{15}N solid-state NMR chemical shift data. The partial proton transfer occurred for an acid−base pair that has a ΔpK_a of 2.09.

The salt−cocrystal continuum is well illustrated by a neutron diffraction study on a pentachlorophenol/4-methylpyridine complex ($\Delta pK_a = 0.77$) at variable temperatures. The data showed that the shared proton moved closer to the oxygen (more cocrystal or non-ionized character) with increasing temperature (Figure 2).[14a,18] Variable temperature neutron diffraction studies were also reported for a carboxylic acid/pyridine 1:2 cocrystal, where the proton in an O···N hydrogen bond moved toward the oxygen with increasing temperature,[19] and for a urea/phosphoric acid 1:1 salt, where the proton showed migration from the urea oxygen to phosphate oxygen with increasing temperature, becoming centered between the acid and base at the highest temperature studied.[20] The variable temperature neutron diffraction studies show that temperature affects the hydrogen location between the donor and acceptor and emphasizes that an ionization state cannot be categorically assigned in some cases. This illustrates the role of factors other than ΔpK_a, in this case temperature, on proton location.

Studies of single-crystal structures of 1:1 pentachlorophenol−amine complexes also illustrate the salt−cocrystal continuum.[14a] The bond length of the phenol C−O group was used to determine the ionic state of the complex. The C−O distance is ∼1.36 Å for the neutral phenol, but is shorter (∼1.26 Å) when the phenolic anion is formed. The 1:1 crystalline complex formed between pentachlorophenol and 3-cyanopyridine, a weak base ($\Delta pK_a = -3.9$), was found to have a C−O bond distance of about 1.3 Å.[14a] Clearly proton transfer does not occur and that complex is a cocrystal. As stronger bases are used as the amine partner in the complexes (ΔpK_a values increase), the C−O distances become shorter. At the other end of the continuum, a complex with the strong base 1,8-bis(dimethylaminomethyl)-naphthalene ($\Delta pK_a = 6.9$) is a salt (C−O ∼ 1.26 Å). Additionally, N···O (between the amine and phenol), O−H (phenol), and N···H (amine) bond lengths also corroborate the conclusions made with C−O bond lengths. A plot correlating C−O bond length and ΔpK_a is shown in Figure 3, demonstrating that a cocrystal is formed at one end of the continuum, and a salt is formed at the other end of the

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Table 1. Structural Data for 2-Aminopyrimidine (**1**) Complexes with Carboxylic Acids

guest	ΔpK_a[a]	ΔpK_a[b]	note[c] (API:guest)	CSD refcode
2-aminobenzoic acid	−1.08		1:2 cocrystal	ZAJJAV
4-aminobenzoic acid	−1.00		1:1 cocrystal	LEWPUY
(+)-camphoric acid	−0.71	−1.31	1:1 cocrystal	KIXVES
indole-3-acetic acid	−0.63		1:1 cocrystal	JIQCAN
indole-2-carboxylic acid	−0.58		1:1 cocrystal	NEXXIX
succinic acid	−0.38	−1.66	1:1 cocrystal	SERMOR, SERMOR10
tetracarboxylic acid	about −0.3		2:1 clathrate, nitrobenzene solvate	KAHMOV
N-methylpyrrole-2-carboxylic acid	−0.30		1:1 cocrystal	JIQCER
p-phenylenediacetic acid	−0.17	−0.83	1:1 cocrystal	GODQIZ
cyclohexane-1,3cis,5cis-tricarboxylic acid	0.14	−1.03, −2.20	1:1 salt	GUTSET
thiophene-2-carboxylic acid	0.35		1:1 cocrystal	JIQCIV
terephthalic acid	0.37	−0.64	1:1 cocrystal	SUVJEY
3-aminobenzoic acid	0.52		1:1 cocrystal	ZAJJEZ
2-naphthoylacetic acid	0.68		1:2 salt + cocrystal	PADZUQ
phenoxyacetic acid	0.69		1:2 (poor crystal quality)[d]	LEWRAG
fumaric acid	0.71	−0.93	1:2 salt + cocrystal[e]	HIQKUN
salicylic acid	0.85		1:1 salt[f]	LEWROU
3,4-dichlorophenoxyacetic acid	0.87		1:1 cocrystal[g]	LEWRIO
2,4-dichlorophenoxyacetic acid	0.88		1:1 cocrystal	LEWREK
naphthalene-1,4-dicarboxylic acid	0.89	−0.22	1:1 cocrystal	OFUHUS
2,5-dichlorophenoxyacetic acid	0.90		1:1 salt	RADFAE
2,3-dichlorophenoxyacetic acid	0.90		1:1 salt	RADGEJ
2,6-dichlorophenoxyacetic acid	0.91		1:1 cocrystal	RADFEI
o-phthalic acid	0.91	−1.54	1:1 cocrystal	ZAJHOH
nitrobenzoic acid	1.61		1:2 salt + cocrystal	ZAJHUN
3,5-dinitrosalicylic acid	2.29		1:1 salt (0.25 EtOH solvate)	AJECIB
2,6-dihydroxybenzoic acid	2.56		1:1 salt	LEWPOS
2,4,6-trinitrobenzoic acid	3.44		1:1 salt	KUFBUI
trichloroacetic acid	3.77		1:1 salt	UGUKEM

[a] pK_a values were calculated as described in the Experimental Section. $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$. pK_a(base) value of 3.86 was used for **1**. [b] ΔpK_a calculated using the second and third pK_a of the acid. [c] Assigned based on CSD structure and ΔD_{C-O} values. The structures reported in the literature are in good agreement with the assignments based on ΔD_{C-O} values, except for LEWRAG, where poor crystal quality does not allow for the determination of ΔD_{C-O} values. [d] Reported as cocrystal. [e] Salt + cocrystal (2-aminopyrimidin-1-ium hemifumarate hemifumaric acid) based on the proton location and bond lengths/angles of the base and acid. The hydrogen donor−acceptor (D−A) length of the ionic interaction is 2.708 Å where D−H is 0.91 Å and H···A is 1.80 Å. [f] **1**:salicylic acid complexes exist in two polymorphic forms, and the single-crystal structure of one of the forms is reported. [g] Reported as cocrystal. The hydrogen donor−acceptor (D−A) length is 2.541 Å where D−H is 1.108 Å and H···A is 1.433 Å.

continuum. However, there are many structures in between that trend smoothly from ionized to non-ionized.

Proton transfer vs ΔpK_a studies were reported describing phenol/amine mixtures in carbon tetrachloride solution.[21] It was determined by infrared spectroscopy measurements that 50% proton transfer occurred for pentachlorophenol−aromatic amine pairs when their ΔpK_a was about 1.6, whereas for chlorophenol−octylamine pairs, the 50% proton transfer in solution occurred at a ΔpK_a of about 3.6.[21a] The pK_a difference as measured in water ($\Delta pK_a = 1.6$) indicates that the ionization state is ∼98% protonated in aqueous solution, whereas in carbon tetrachloride it was only 50%. Thus, ΔpK_a values measured in water do not necessarily correspond to the amount of proton transfer in nonaqueous environments.

2-Aminopyrimidine (**1**, Figure 1) is a weakly basic compound with a calculated pK_a of 3.86. A number of salts and cocrystals of **1** containing carboxylic acids are reported in the Cambridge Structural Database (CSD).[22] Table 1 lists the carboxylic acids in these complexes in the order of increasing ΔpK_a values relative to **1**. Based on the C−O distances, D_{C-O}, of the carboxyl group of the guest molecules, a distinction between salts and cocrystals can be made as a carboxyl anion possesses two similar D_{C-O} values

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(22) Lynch, D. E.; Smith, G.; Freney, D.; Byriel, K. A.; Kennard, C. H. L. Molecular Cocrystals of Carboxylic-Acids. XV. Preparation and Characterization of Heterocyclic Base Adducts with a Series of Carboxylic-Acids, and the Crystal-Structures of the Adducts of 2-Aminopyrimidine with 2,6-Dihydroxybenzoic Acid, 4-Aminobenzoic Acid, Phenoxyacetic Acid, (2,4-Dichlorophenoxy)-Acetic Acid, (3,4-Dichlorophenoxy)-Acetic Acid and Salicylic-Acid, and 2-Aminopyridine with 2,6-Dihydroxybenzoic Acid. *Aust. J. Chem.* **1994**, *47*, 1097−1115.

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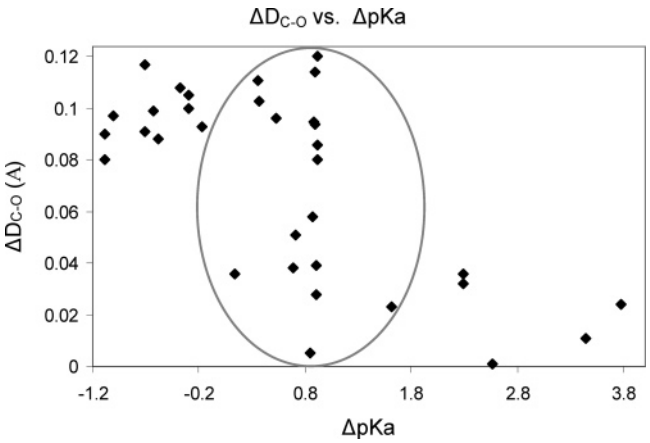

Figure 4. A plot of ΔpK_a vs ΔD_{C-O} values for complexes of **1** where ΔD_{C-O} = difference between the two C−O distances in the carboxylic acids in the complex. The ΔD_{C-O} values of carboxylates were used when the complex contained both ionic and neutral carboxylic acids (refcodes PADZUQ, HIQKUN, LEWRIO, and ZAJHUN), and LEWRAG was not included due to the data quality.

(ΔD_{C-O} < 0.03 Å), whereas a neutral carboxyl group possesses two distinctively different D_{C-O} values (ΔD_{C-O} > 0.08 Å).[14b] This assignment correlates well with the reported structure in the literature (see the CSD refcode in Table 1). Therefore, complexes with ΔD_{C-O} < 0.03 Å are salts, and complexes with ΔD_{C-O} > 0.08 Å are cocrystals.

A plot of ΔD_{C-O} values vs ΔpK_a values for complexes of **1** is shown in Figure 3. At high ΔpK_a, salts are formed as indicated by the small ΔD_{C-O} values; at negative ΔpK_a, cocrystals are formed as indicated by the large ΔD_{C-O} values. However, for the complexes with ΔpK_a values between 0 and 2 (circled region in Figure 4), seven salts (proton transferred) and eight cocrystals (proton not transferred) were found.

The ordering of the 2-aminopyrimidine complexes by ΔpK_a in Table 1 and the corresponding salt/cocrystal label assigned on the basis of C−O distances indicate that, for ΔpK_a values of 0 to about 2, there is very little correlation between ΔpK_a and the ionization state of the crystalline complexes of **2**. In the narrow transition region where salts and cocrystals overlap, the type of resulting complex appears to be random, suggesting that pK_a is not a good predictive tool in this ΔpK_a region.

The unpredictable ionization states in this region cannot be attributed simply to the poor correlation between pK_a and proton transfer in the solid state. The molecular environment of each crystal structure is unique and can affect the amount of proton transfer that occurs. In much the same way as it is possible to alter the amount of proton transfer by changing solvent,[23] it is possible to affect the protonation state of an acid−base molecular complex by changing the crystalline environment.

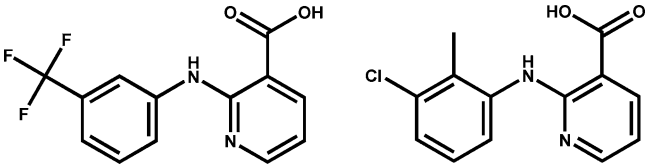

Figure 5. Molecular structures of niflumic acid (left) and clonixin (right).

It is possible to observe different ionization states for the same acid−base pair if multiple solid forms of that acid−base complex are isolated. In one crystal structure the acid and base may be non-ionized while in a different crystal structure the same acid and base can be ionized. This situation applies to acid−base pairs within the narrow ΔpK_a transition region that separates salts from cocrystals, and there are a number of known examples in the literature that illustrate this point. For example, pyridine and formic acid can form either a cocrystal as a 1:1 complex or a salt as a 1:4 complex,[24] pyridine and 3,5-dinitrobenzoic acid form either a cocrystal as a 1:2 complex or a salt as a 1:1:1 complex with water,[25] and 2,3-lutidine and fumaric acid form either a cocrystal as a 2:1 complex or a salt as a 1:2 complex.[26] Similarly, 1,2-diazabicyclo[2,2,2]octane forms crystalline complexes with a series of dicarboxylic acids in which the carbon chain length of the dicarboxylic acid influences whether a salt or cocrystal results.[27]

The influence of the crystal structure on ionization state is also evident in the reported crystal structures of four clonixin polymorphs.[7d,28] Clonixin (2-(2-methyl-3-chloroanilino)-nicotinic acid, Figure 5) contains both a pyridine base and a carboxylic acid group and is capable of forming a zwitterion. Of the four structures of clonixin in the CSD,[29] two polymorphs form acid−base hydrogen bonds between the carboxylic acid and the pyridine, and the other two polymorphs form a carboxylic acid hydrogen bonded dimer.[7d] Of the two polymorphs with an acid−base interaction, one is ionized (a zwitterion) while the other one is non-ionized (Figure 6). Both of these structures were determined at room

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(28) Takasuka, M.; Nakai, H.; Shiro, M. Infrared Spectral and X-Ray Studies of Polymorphic Forms of 2-(2-methyl-3-chloroanilino) nicotinic Acid. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1061−1067.

(29) CSD refcodes BIXGIY, BIXGIY02, BIXGIY03, and BIXGIY04.

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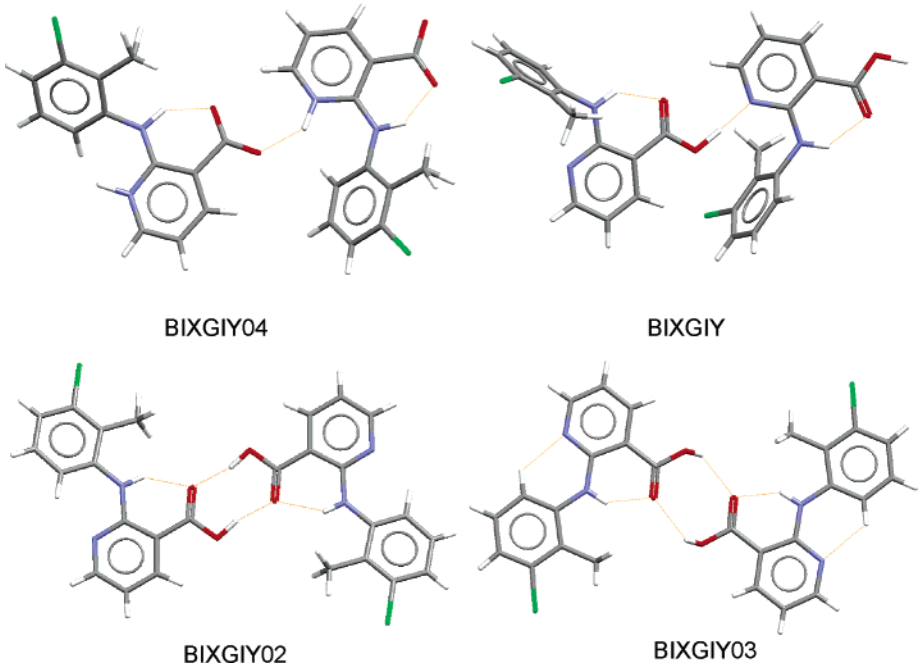

Figure 6. Four clonixin polymorph crystal structures demonstrate that the same molecule can adopt a variety of hydrogen bonding motifs and ionization states. BIXGIY04 and BIXGIY exhibit acid−base hydrogen bonds whereas BIXGIY02 and BIXGIY03 exhibit acid−acid hydrogen bonds. BIXGIY04 contains zwitterionic clonixin molecules while the other three polymorphs contain non-ionized molecules.

temperature, and the C−O bond distances confirm the ionization states. These examples demonstrate that the protonation state observed in a crystal structure is affected not only by the acid and base strength but also by the crystalline environment.

An API that is structurally related to clonixin is niflumic acid (2-(3-(trifluoromethyl)anilino)-nicotinic acid, Figure 5). The calculated pK_a values for clonixin (1.69 and 4.80) and niflumic acid (1.70 and 4.71) are nearly identical, suggesting that the acid−base behavior should be comparable. While there are four crystal structures of clonixin polymorphs in the CSD, only one crystalline form of niflumic acid has been characterized by single-crystal X-ray diffraction (CSD refcode NIFLUM10[30]), and no polymorphs of niflumic acid are known.[31] The crystal structure of niflumic acid has a hydrogen bonding motif that is similar to clonixin structures BIXGIY02 and BIXGIY03 in which the acid group is involved in a homomolecular acid−acid pairing. On the basis of the structural similarity and pK_a values, it is reasonable to assume that niflumic acid is also capable of forming polymorphs with mixed ionization states.

Consider a complex of niflumic acid with an acid counterion/guest that has a pK_a value that is similar to the acid group on the API. For instance, the pK_a of maleic acid

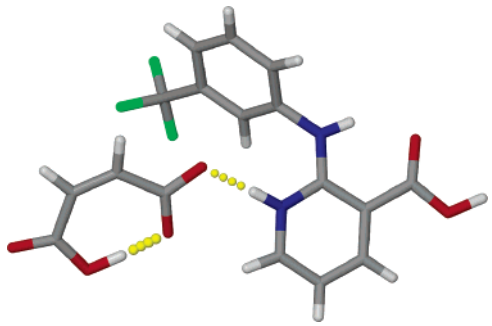

Figure 7. Molecular diagram of the niflumic acid:maleic acid salt (**10**).

(pK_{a1} = 1.91) is similar to the pK_a of the acid group on niflumic acid (pK_a = 1.70). Is a complex of niflumic acid and maleic acid expected to be a salt or a cocrystal? The ΔpK_a for niflumic acid (pK_a = 4.71) and maleic acid (pK_{a1} = 1.91) is 2.8, which suggests that the ionization state in a crystalline solid is unpredictable. It is suggested that a niflumic acid−maleic acid complex would be capable of forming non-ionized or ionized complexes even though the solid form that we obtained containing 1:1 niflumic acid: maleic acid (**10**, Figure 7) is a salt based on the proton location and C−O bond distances. That the salt was observed in the structure reported here should not suggest that non-ionized complexes of niflumic acid and maleic acid could not be isolated, nor that a complex of clonixin and maleic acid will be a salt rather than a cocrystal.

Although the ionization state of a zwitterion in a crystal structure (intramolecular proton transfer) is not directly related to the discussion of salt formation between two

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independent molecules (intermolecular proton transfer), the previous examples support the idea that ionization state is influenced directly by the crystal structure. Additional evidence can be found in crystals containing piroxicam. Piroxicam has one tautomeric form that is non-ionized and one that is a zwitterion. The anhydrous polymorphs of piroxicam contain the non-ionized tautomer while piroxicam monohydrate contains the zwitterionic tautomer.[32] We have studied cocrystal formation with piroxicam,[33] and in one surprising example we found that crystal structures of two polymorphs of a 1:1 piroxicam:4-hydroxybenzoic acid cocrystal showed that one polymorph contained the non-ionized piroxicam tautomer and the non-ionized acid guest and the second polymorph contained the zwitterion tautomer of piroxicam and the non-ionized guest. Any measure of acid−base strength cannot adequately predict the ionization state in a crystalline solid if it is possible for the same components to crystallize as true polymorphs with different ionization states. As part of our continuing study of cocrystals and their properties, we carried out a search for cocrystals of theophylline (**2**) and found 11 previously unknown complexes. Theophylline (**2**) has been administered in its native state under a variety of trade names and as noncovalent derivatives with ethanolamine (Lilly's Monotheamine), lysine (Malesci's Paidomal), sodium acetate (Winthrop's Theocin), sodium glycinate (Lorex's Biophylline and others), ethylenediamine hydrate (aminophylline), 2-amino-2-methyl-2-propanol (butaphyllamine), and choline (choline theophyllinate). Some of these derivatives are described as salts, and others are simply called a "compound with" theophylline.[34] Theophylline is amphiprotic (can donate or accept a proton) and cocrystallizes with a wide range of guest molecules. Complexes of **2** in which the guest is acidic are listed in Table 2, and complexes of **2** in which the guest is basic are listed in Table 3. In each table the complexes are listed by increasing ΔpK_a values which were calculated with respect to theophylline (base $pK_a = 1.7$, acid $pK_a = 8.6$).

Forty-one unique theophylline complexes were found in the literature, and structures of 16 have been characterized by single-crystal X-ray diffraction.[35] We determined single-crystal structures of three new theophylline cocrystals (**3**, **5**, and **6**, Table 4) and prepared and characterized seven other new complexes by XRPD and IR (benzoic acid, glycolic acid, 2,4-dihydroxybenzoic acid, gentisic acid, chloroacetic acid, 5-chlorosalicylic, anhydrous 1,7-heptanediamine). The complexes of theophylline and acetaminophen[36] were previously reported (**7**, Table 4). The crystalline form of theophylline with 5-chlorosalicylic acid we obtained was different from the structure of this complex that was previously reported.[37] The single-crystal structure was determined for a theophylline−salicylic acid cocrystal whose IR spectroscopy was previously reported (**4**, Table 4).[38g] In addition, single-crystal structures of two known ethylenediamine complexes, anhydrous and hydrate, were determined (**8** and **9**, respectively, Table 4). As X-ray crystal structures are not available for all of the known theophylline organic salts and cocrystals,[38] IR spectroscopic data were utilized to evaluate the ionization state of the complexes that have no reported single-crystal data.

Theophylline contains two carbonyl groups and a secondary amine. The anhydrous crystal exhibits IR bands at 1717, 1668 (carbonyl groups), and 3122 cm^{-1} (secondary amine).[38d]

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(33) Childs, S. L. and Hardcastle, K. I. Cocrystals of piroxicam with carboxylic acids. *Cryst. Growth Des.*, in press.

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Table 2. Theophylline (**2**):Acid Complexes Listed by Increasing ΔpK_a Values

acid guest	ΔpK_a[a]	note (API:guest)[b]	IR[c]	CSD refcode
none (**2**)		anhydrate		BAPLOT, BAPLOT01
		metastable anhydrate[43]		
2:water		monohydrate		THEOPH01
acetaminophen	−8.2	1:1 cocrystal		**7** (Table 4)
salicylamide	−6.7	1:1 cocrystal by IR[38f]		
3-nitrophenol	−6.6	1:1 cocrystal by IR[38f]		
sulfathiazole	−5.5	1:1 cocrystal		SULTHE
4-nitrophenol	−5.5	1:1 cocrystal, IR[38f]		TOPPNP
2-nitrophenol	−5.4	1:1 cocrystal by IR[38f]		
ethylenediamine carbamate	−3.0	1:1 cocrystal by IR,[38g] carbamate zwitterion		WUYROX
sorbic acid	−2.9	1:1 cocrystal by IR	yes	**3** (Table 4)
4-hydroxybenzoic acid	−2.9	1:1 cocrystal by IR	yes	**6** (Table 4)
glutaric acid	−2.6	1:1 cocrystal, by IR[38e]		see ref 39
benzoic acid	−2.5	1:1[d] cocrystal	yes	
3-chlorobenzoic acid	−2.1	1:1 cocrystal by IR[38f]		
glycolic acid	−2.0	1:1[d] cocrystal	yes	
3-nitrobenzoic acid	−1.8	1:1 cocrystal by IR[38f]		
4-nitrobenzoic acid	−1.7	1:1 cocrystal by IR[38f]		
2,4-dihydroxybenzoic acid	−1.6	1:1[d] cocrystal	yes	
maleic acid	−1.5	1:1 cocrystal, by IR[38e]		see ref 39
1-hydroxy-2-naphthoic acid	−1.3	1:1 cocrystal	yes	**5** (Table 4)
salicylic acid	−1.3	1:1 cocrystal by IR[38f,g]	yes	**4** (Table 4)
gentisic acid	−1.3	1:1[d] cocrystal	yes	
malonic acid	−1.2	1:1 cocrystal, by IR[38e]	yes	see ref 39
3,5-dinitrobenzoic acid	−1.1	1:1 cocrystal by IR[38f]		
chloroacetic acid	−1.0	1:1[c] cocrystal	yes	
5-chlorosalicylic acid	−0.9	1:1 cocrystal		CSATEO
		1:1[d] cocrystal, different from CSATEO by XRPD	yes	
2-nitrobenzoic acid	−0.5	1:1 cocrystal by IR[38f]		
oxalic acid	0.3	2:1 cocrystal, by IR[38e]		see ref 39
5-sulfosalicylic acid	2.3	1:1:1 salt by IR[38g]		WUYRUD
HCl	9.7	1:1 salt (poor data)		THEOPI

[a] $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$. Theophylline pK_a value of 1.7 (conjugate base) was used. [b] Molar ratio of the complexes is given in the following order: theophylline:guest:water. For the cocrystals and salts that were identified by infrared spectroscopy (IR) were noted, the results were consistent with the CSD structure where the data are available. [c] IR spectroscopy (current study) was used to make salt vs cocrystal assignments where X-ray structures were not obtained. [d] Molar ratio confirmed by proton NMR spectroscopy in DMSO-d_6.

When a salt is formed with amine bases, the carbonyl bands are shifted to lower frequencies by 30 to 40 cm^{-1}.[38c,d,g,i,l] In addition, the NH stretching bands corresponding to the amine base are not observed in a salt (NH and NH_2 are normally between 3200 and 3500 cm^{-1}); instead, the corresponding ammonium signals of the amine base are present (NH_3^+ is normally between 2000 and 2200 cm^{-1}).[38g,k,l] On the other hand, when a salt is formed with an acid, the protonated amine band of the theophyllium ion occurs near 3147 cm^{-1} and the carbonyl band of the theophyllium ion remains similar to that of anhydrous theophylline.[38g] In theophylline cocrystals, the theophylline NH and carbonyls are shifted due to hydrogen bonding, but the magnitude of the shift is relatively small. For example, the carbonyl bands are typically shifted lower by about 10 to 20 cm^{-1}.[38f,g,h,k] In theophylline cocrystals with carboxylic acid guests, the O−H stretch of a carboxylic acid hydrogen bonded to a theophylline nitrogen atom (COOH···N) is reported to be near 2500 and the H···N stretch of COOH···N is reported to be near 1900 cm^{-1}.[16i] The correlation between IR data and the nature of theophylline complexes is evident where both IR and single-crystal diffraction data exist. Recently, crystal structures of cocrystals of **2** with glutaric acid, maleic acid, malonic acid, and oxalic acid were reported,[39] and the structural data confirmed a previous report in which IR spectroscopy was used to characterize these complexes.[38e]

Of the known complexes containing theophylline and acids, all are cocrystals except for those containing 5-sulfosalicylic acid and hydrochloric acid, which are salts (Table 2). The pK_a of the conjugate base of **2** is 1.7, and the resulting ΔpK_a values for cocrystals containing acids were negative except for oxalic acid, which has a ΔpK_a of 0.3. The single-crystal structures and IR data for complexes of **2** with acidic guest compounds reported here indicate that each is a

(39) Trask, A. V.; Motherwell, W. D.; Jones, W. Physical stability enhancement of theophylline via cocrystallization. *Int. J. Pharm.* **2006**, *320*, 114−123.

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Table 3. Theophylline (**2**):Base Complexes Listed by Increasing ΔpK_a Values

base guest	ΔpK_a[a]	note (API:guest)[b]	IR[c]	CSD refcode
urea	−8.5	1:1 cocrystal		DUXZAX
4-nitroaniline	−7.6	1:1 cocrystal		ZEXTIF
triethanolamine	−0.8	no structure information available[44]		
5-fluorouracil	−0.7	2:1:1 cocrystal		ZAYLOA
1,10-phenanthroline	−3.4	1:1 cocrystal by IR[38g]		
phenobarbital	−1.0	2:1 cocrystal		THOPBA
diethanolamine	0.1	no structure information available[45]		
isopropanolamine	0.6	no structure information available[34c]		
2-amino-2-methyl-1-propanol	0.6	1:1[c] salt[46]	yes	
ethanolamine	0.6	1:1 salt by IR[38g]	yes	WUYRIR
2-aminobutanol	0.7	salt (no structure information available)		
benzylamine	0.8	1:1 cocrystal by IR[38h]		
lysine	0.9	1:1 salt[47] (no structure information available)		
arginine	1.0	1:1:1 salt[47a]		
n-propylamine	1.3	1:1 salt by IR[38i]		
ethylenediamine	1.3,	2:1 mixed ionization states by X-ray structure	yes	**8** (Table 4)
	1.7	2:1:1 hydrate, salt by IR[34a,38k]	yes	**9** (Table 4)
piperazine	1.3,	hydrate[34a] (no structure information available)[d]		
	3.3	1:2[c] appears to be salt	yes	
1,3-propanediamine	1.8, 0.0	2:1:1 salt by IR[38k]		
ethylamine	2.0	1:1 salt by IR[38i]		
1,4-butanediamine	2.1, 0.7	2:1 salt[34a] by IR [38k,l]		YAHQII
methylamine	2.1	1:1:1 salt by IR[38i]		
1,5-pentanediamine	2.3, 1.1	2:1:2 salt[34a] by IR[38k]	yes	
1,6-hexanediamine	2.3, 1.5	2:1 salt[34a] by IR[38k]		
1,7-heptanediamine	2.4,	2:1:1 hydrate mixed ionization states by IR[38k]	yes	
	1.7	anhydrous salt	yes	
1,8-octanediamine	2.4, 1.7	2:1 salt by IR[38k]		
choline	5.3	1:1 salt (reacted with NaOH)[34d]		

[a] $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$. Theophylline pK_a value of 8.6 (acid) was used. The values in the second ΔpK_a column were calculated using the second pK_a values of bases. [b] Molar ratio of the complexes is given in the following order: theophylline:guest:water. For the cocrystals and salts that were identified by infrared spectroscopy (IR) were noted, the results were consistent with the CSD structure where the data are available. [c] IR spectroscopy (current study) was used to make salt vs cocrystal assignments where X-ray structures were not obtained. [d] Molar ratio confirmed by proton NMR spectroscopy in DMSO-d_6.

cocrystal. In addition, new complexes of **2** with benzoic acid, glycolic acid, 2,4-dihydroxybenzoic acid, gentisic acid, and chloroacetic acid were prepared and determined to be cocrystals based on IR data. A complex of **2**:5-chlorosalicylic acid isolated as part of this study yielded a crystalline form different from the reported structure (refcode CSATEO[37]) in the Cambridge Structural Database (CSD) based on XRPD data, but both of these solid forms are cocrystals based on IR data.

The salt/cocrystal classification for each **2**:amine base complex based on single-crystal data, IR data collected as part of this study, and IR data obtained from the literature is shown in Table 3. Two crystal structures of **2**:ethylenediamine are reported here, and a total of six single-crystal structures containing theophylline and an amine base were obtained from the literature. Samples of **2**:2-amino-2-methyl-1-propanol, **2**:ethanolamine, **2**:piperazine, **2**:1,5-pentanediamine, and **2**:1,7-heptanediamine (the reported hydrate form and a new anhydrate) were isolated as part of this study, and IR and XRPD data were obtained.

The most intriguing structure we investigated was that of **2**:ethylenediamine. The generic name of this complex is aminophylline, which exists as a hydrate (**9**, Table 4) and an anhydrate (**8**, Table 4). Aminophylline hydrate is the commercial form of aminophylline. It has historically been described as a "compound with" theophylline,[40] a salt, or a complex containing 2:1:1 theophylline:ethylenediamine:water. The ambiguity is warranted because our results demonstrate that while the commercial form (aminophylline hydrate) is clearly a salt, the anhydrate contains both ionized and non-ionized components.

The single-crystal structures of anhydrous aminophylline and aminophylline hydrate are reported here. The protons in these structures were located in the difference maps and refined with isotropic U_{ij}'s related to the atom to which they are bonded. Aminophylline hydrate (**9**) has two unique theophylline molecules and two unique ethylenediamine halves (each of which is completed by an inversion center) along with one water molecule in the asymmetric unit (2:1:1 theophylline:ethylenediamine:water). The structure refine-

(40) O'Neil, M. J.; Merck & Co., *The Merck index: an encyclopedia of chemicals, drugs, and biologicals*, 13th ed.; Merck: Whitehouse Station, NJ, 2001.

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Table 4. Crystallographic Data for **3**−**10**

	3	**4**	**5**	**6**
identification code	**2**:sorbic acid	**2**:salicylic acid	**2**:1-hydroxy-2-naphthoic acid	**2**:4-hydroxybenzoic acid
empirical formula	$C_{13}H_{16}N_4O_4$	$C_{14}H_{15}N_4O_5$	$C_{36}H_{32}N_8O_{10}$	$C_{14}H_{14}N_4O_5$
formula weight	292.30	319.30	736.70	318.29
temperature (K)	100(2)	100(2)	173(2)	173(2)
wavelength (Å)	1.541 78	1.541 78	1.541 78	1.541 78
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
space group	*P*2(1)/*m*	*P*2(1)/*n*	*P*2(1)/*c*	*P*2(1)/*c*
unit cell dimens				
a (Å)	8.7478(2)	6.9183(3)	11.814(3)	7.1201(18)
b (Å)	6.53610(10)	25.9086(10)	31.707(8)	7.928(2)
c (Å)	12.5842(2)	7.9749(4)	8.920(2)	24.763(6)
α (deg)	90	90	90	90
β (deg)	107.2960(10)	104.754(3)	98.072(7)	91.660(7)
γ (deg)	90	90	90	90
volume (Å^3)	686.98(2)	1382.32(11)	3308.1(15)	1397.2(6)
Z	2	4	4	4
density (calcd) (Mg/m^3)	1.413	1.534	1.479	1.513
absorption coeff (mm^{-1})	0.899	1.007	0.929	0.996
F(000)	308	668	1536	664
cryst size (mm^3)	0.39 × 0.17 × 0.09	0.33 × 0.03 × 0.03	0.15 × 0.098 × 0.05	0.20 × 0.10 × 0.03
θ range for data collection(deg)	3.68−66.67	3.41−65.68	2.79−67.02	7.75−42.31
index ranges	$-10 \le h \le 9$, $-7 \le k \le 7$, $-14 \le l \le 14$	$-7 \le h \le 6$, $-19 \le k \le 30$, $-7 \le l \le 8$	$-10 \le h \le 13$, $-32 \le k \le 37$, $-9 \le l \le 8$	$-6 \le h \le 5$, $-6 \le k \le 6$, $-21 \le l \le 19$
reflns collected	3329	3694	12736	2502
indep reflns	1261 [*R*(int) = 0.0536]	1396 [*R*(int) = 0.0605]	5009 [*R*(int) = 0.1146]	905 [*R*(int) = 0.0970]
completeness (%)	95.1	58.3	84.8	92.6
absorption correction	none	none	none	none
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least- squares on F^2
data/restraints/params	1261/0/137	1396/0/213	5009/0/505	905/0/242
GOF on F2	1.192	1.002	0.914	1.011
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0381, wR2 = 0.1005	R1 = 0.0516, wR2 = 0.1126	R1 = 0.0691, wR2 = 0.1552	R1 = 0.0361, wR2 = 0.0792
R indices (all data)	R1 = 0.0454, wR2 = 0.1221	R1 = 0.0783, wR2 = 0.1205	R1 = 0.1869, wR2 = 0.2111	R1 = 0.0637, wR2 = 0.0863
largest diff peak/hole (e Å^{-3})	0.262/−0.228	0.258/−0.204	0.347/−0.352	0.131/−0.207

	7	**8**	**9**	**10**
identification code	**2**:acetominophen	aminophylline anhydrous	aminophylline hydrate	niflumic acid:maleic acid
empirical formula	$C_{15}H_{17}N_5O_4$	$C_{16}H_{24}N_{10}O_4$	$C_{16}H_{26}N_{10}O_5$	$C_{17}H_{13}F_3N_2O_6$
formula weight	331.34	420.45	438.47	398.29
temp (K)	100(2)	173(2)	173(2)	173(2)
wavelength (Å)	1.541 78	1.541 78	1.541 78	1.541 78
crystal system	monoclinic	monoclinic	triclinic	monoclinic
space group	*P*2(1)/*n*	*P*2(1)/c	$P\bar{1}$	*P*2(1)/*c*
unit cell dimens				
a (Å)	8.7337(2)	8.7804(5)	8.3936(7)	8.1434(5)
b (Å)	15.3838(3)	6.5989(4)	10.2277(6)	20.7559(11)
c (Å)	11.5271(3)	16.0041(10)	11.8295(6)	10.6511(7)
α (deg)	90	90	78.839(3)	90
β (deg)	99.256(2)	102.292(4)	77.795(4)	110.276(3)
γ (deg)	90	90	81.075(4)	90
volume (Å^3)	1528.59(6)	906.04(9)	966.87(11)	1688.73(18)
Z	4	2	2	4
density (calcd) (Mg/m^3)	1.440	1.541	1.506	1.567
absorption coeff (mm^{-1})	0.900	0.971	0.973	1.232
F(000)	696	444	464	816
cryst size (mm^3)	0.20 × 0.16 × 0.10	0.23 × 0.19 × 0.06	0.22 × 0.12 × 0.07	0.26 × 0.20 × 0.16
θ range for data collection (deg)	7.50−66.12	5.16−66.25	5.39−66.51	4.26−66.70
index ranges	$-7 \le h \le 10$, $-18 \le k \le 18$, $-13 \le l \le 13$	$-10 \le h \le 10$, $-7 \le k \le 7$, $-18 \le l \le 18$	$-7 \le h \le 7$, $-10 \le k \le 12$, $-9 \le l \le 14$	$-9 \le h \le 8$, $-22 \le k \le 24$, $-11 \le l \le 12$
reflns collected	6265	3663	2826	8182
indep reflns	2189 [*R*(int) = 0.0625]	1446 [*R*(int) = 0.0374]	1763 [*R*(int) = 0.0434]	2754 [*R*(int) = 0.0705]
completeness (%)	81.9	91.1	51.9	91.9
absorption correction	none	semiempirical from equivalents	none	none
refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2
data/restraints/params	2189/0/224	1446/0/150	1763/0/294	2754/0/305
GOF on F2	1.168	1.035	1.050	1.060
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0441, wR2 = 0.1221	R1 = 0.0807, wR2 = 0.2574	R1 = 0.0366, wR2 = 0.0939	R1 = 0.0531, wR2 = 0.1058
R indices (all data)	R1 = 0.0607, wR2 = 0.1505	R1 = 0.0952, wR2 = 0.2674	R1 = 0.0396, wR2 = 0.0962	R1 = 0.0778, wR2 = 0.1118
largest diff peak/hole (e Å^{-3})	0.253/−0.333	0.349/−0.392	0.268/−0.367	0.416/−0.452

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Atoms	Bond length
N2C–H2C3	0.891 Å
O1–H2C3	2.009 Å
N2C–H2C4	0.970 Å
O1S–H2C4	1.789 Å
N2C–H2C5	1.026 Å
N2B–H2C5	1.772 Å
O1S–H1S	0.817 Å
N1–H1S	2.047 Å
O1S–H2S	0.943 Å
N1B–H2S	1.874 Å
N1C–H1C3	0.935 Å
O2–H1C3	1.915 Å
N1C–H1C4	1.128 Å
N2–H1C4	1.651 Å
N1C–H1C5	0.878 Å
O2B–H1C5	2.055 Å

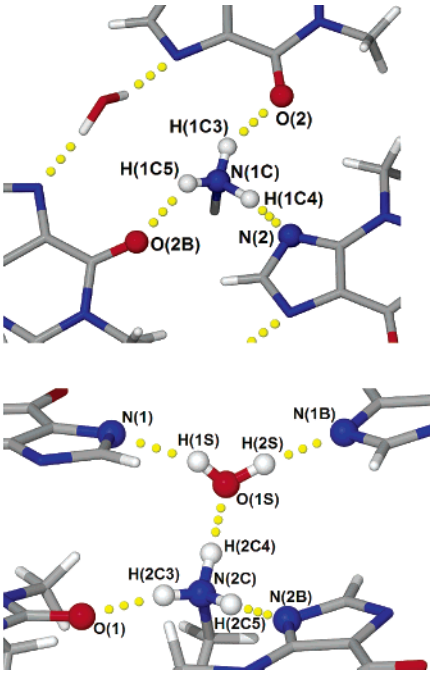

Figure 8. The asymmetric unit of aminophylline hydrate (**9**) contains two independent theophylline molecules, one water molecule, and two independent halves of ethylenediamine molecules resulting in two unique amine environments. Selected bond distances in **9** are shown.

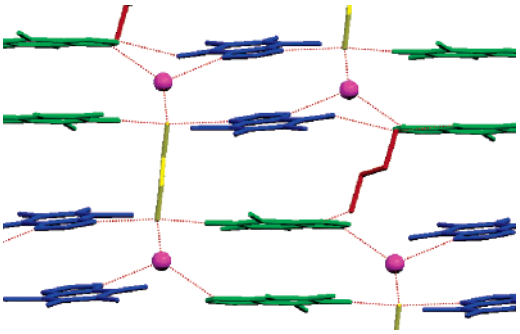

Figure 9. The theophylline molecules in **9** are layered with the ethylenediamine cations connecting the layers. Symmetry equivalent molecules are colored the same, and hydrogen bonds between heteroatoms are shown. Hydrogen atoms are omitted for clarity.

ment indicates that both of the independent acid−base interactions are ionized. There is no indication from the final difference map that the nitrogen atoms on the theophylline imidazole ring have covalently bonded protons. Although some of the long N−H bond lengths suggest that the ionization state is tenuous (Figure 8, up to 1.128 Å for one acid−base interaction), proton transfer has occurred and the protons are located on the nitrogen base with no residual electron density found near the theophylline. A packing diagram for **9** is shown in Figure 9.

While aminophylline hydrate contains only ionized acid−base interactions, anhydrous aminophylline (**8**) revealed a unique solid-state equilibrium in which the acidic proton location was disordered and the structure contains both ionized and non-ionized components. Bond distances for the amine interactions are shown in Figure 10. A packing diagram for **8** is shown in Figure 11. The refinement resulted in 75% ionized and 25% non-ionized components, but the situation is complicated by the fact that the non-ionized components are further distributed between two equally shared non-ionized states (Figure 12). Regardless of the disorder, the presence of N−H groups on the theophylline confirms that there is a non-ionized component in the structure of anhydrous aminophylline. It does not seem appropriate to assign a salt or cocrystal label to the anhydrous aminophylline structure because it contains mixed ionization states. What is important in this case is not defining aminophylline as a salt or a cocrystal, but rather noting that the ionization state of the same acid−base complex can change depending on the crystal structure.

The mixed ionization states observed in the single-crystal structures of aminophylline are also observed in the IR data for these complexes (Figure 13). The IR stretching bands corresponding to carbonyls of aminophylline hydrate are shifted by −32 and −28 cm^{-1}, respectively, indicating salt formation. The IR bands corresponding to carbonyls of anhydrous aminophylline exhibit multiple sets, with the non-ionized component showing a shift of −10 and −17 cm^{-1} and the ionized component −29 and −38 cm^{-1}, suggesting that the sample contains both ionized and non-ionized interactions.

An example similar to the aminophylline system is observed in two **2**:1,7-heptanediamine complexes (ΔpK_a = 1.7 and 2.4). The hydrated **2**:1,7-heptanediamine complex was first reported by Nishijo.[38k] In the course of preparing

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Atoms	Bond length
N2–H2D	0.844 Å
N1B–H2B3	0.904 Å
N2–H2B3	1.932 Å
H2D–H2B3	1.390 Å
N1B–H2B2	0.874 Å
O2–H2B2	1.995 Å
N1B–H2B1	0.962 Å
N1–H2B1	2.000 Å

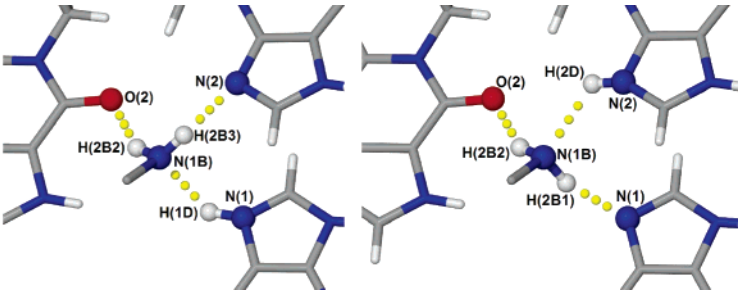

Figure 10. The asymmetric unit of anhydrous aminophylline (**8**) contains one theophylline molecule and one half of one ethylenediamine molecule. Selected bond distances are shown for two disordered states.

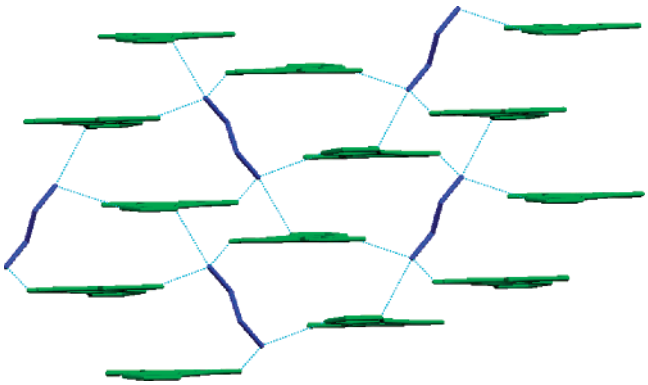

Figure 11. A packing diagram of **8**. Symmetry equivalent molecules are colored the same, and hydrogen bonds between heteroatoms are shown. Hydrogen atoms are omitted for clarity.

samples of this **2**:1,7-heptanediamine complex we obtained a solid that matched the reported IR spectrum and XRPD pattern of the hydrate by isolating material from a solution containing water.[41] We also obtained a new anhydrous form from a grinding experiment containing a 2:1 molar ratio of **2**:1,7-heptanediamine. In this system, the hydrate contains both ionized and non-ionized components while the anhydrous material is ionized based on IR spectroscopy (Figure 14). This is opposite of the results observed with aminophylline, suggesting that the presence of the water or the hydrogen bonding effect does not necessarily predispose the complex to being a salt or a cocrystal but rather the change in polarity that accompanies the inclusion or exclusion of water and the subsequent change in crystal structure environment are responsible for the different ionization states in these cases.

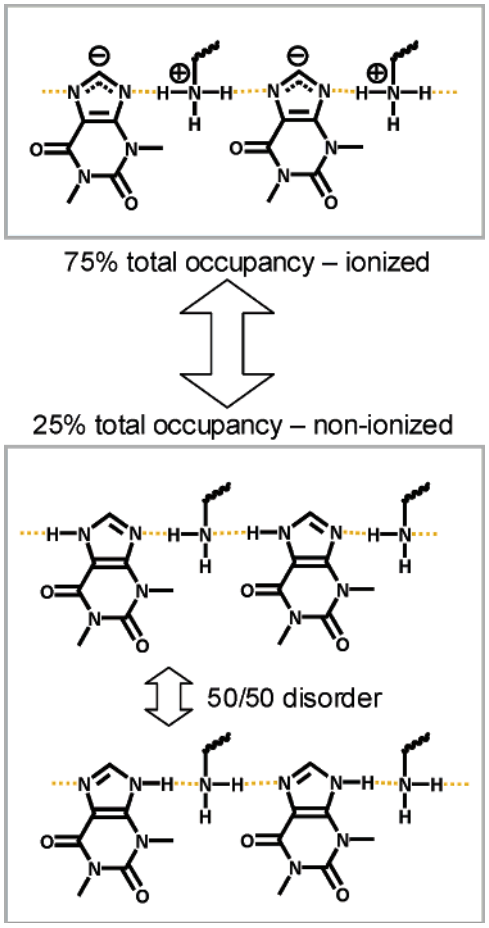

Figure 12. Disorder modeling in anhydrous aminophylline (**8**) indicates that 75% of the structure contains ionized components and 25% contains non-ionized components. Of the 25% occupancy containing non-ionized components, there is an even distribution between two non-ionized disordered states.

Conclusions

When an acid and a base cocrystallize, both the acid and base strengths and the crystalline environment determine the extent of proton transfer. The structures of aminophylline hydrate and anhydrate reported here clearly demonstrate that in a different crystal environment the protonation state of the same acid−base pair can change.

The majority of multicomponent crystals containing an acid and a base can be classified as a salt or a cocrystal based on the proton location as determined from single-crystal diffraction experiments or from spectroscopic data. However, in some cases it is not possible to classify a solid form as a salt or a cocrystal because either the proton is shared or the

(41) The solid that we obtained contained a small amount of theophylline along with the theophylline:1,7-heptanediamine hydrate complex. This was confirmed by comparing the XRPD data reported by Nishijo to the XRPD data for the sample we isolated. The IR data for our sample also shows a theophylline component. Taking this into account, the conclusion that mixed ionization states are present in the theophylline:1,7-heptanediamine hydrate complex is still valid.

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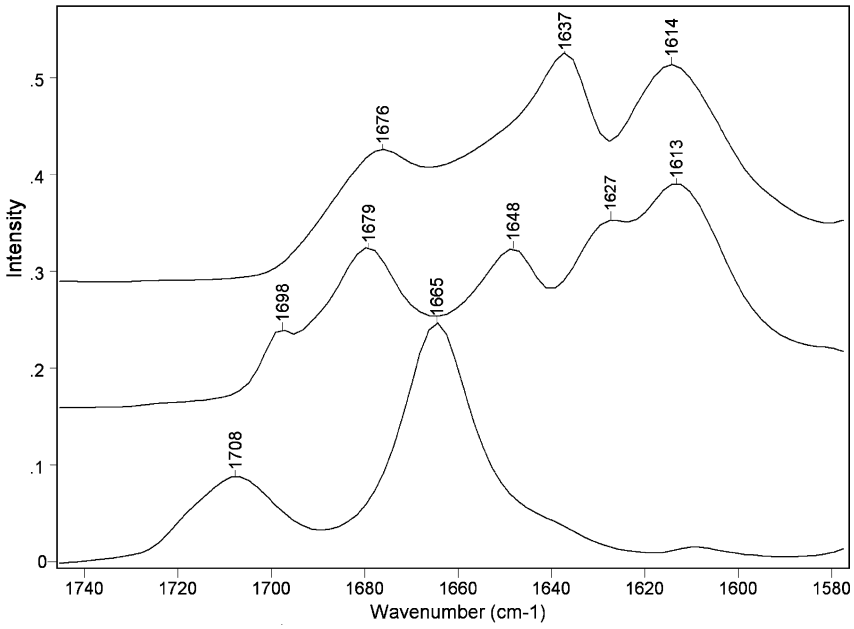

Figure 13. IR bands in the carbonyl region for aminophylline hydrate (top, **9**), anhydrous aminophylline (middle, **8**), and theophylline anhydrate (bottom, **1**).

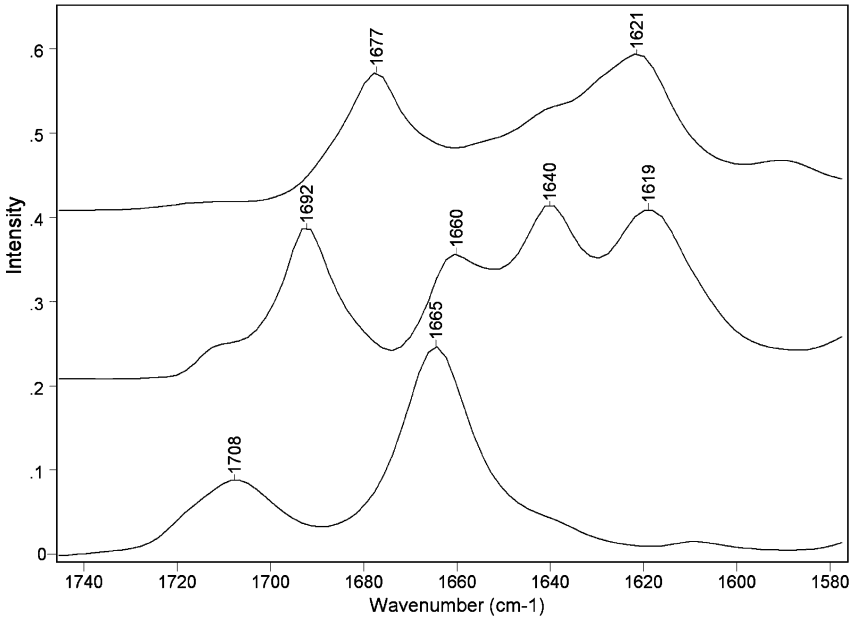

Figure 14. IR bands in the carbonyl region for anhydrous theophylline:1,7-diaminoheptane (top), theophylline:1,7-diaminoheptane hydrate (middle), and theophylline anhydrate (bottom, **1**).

structure contains disordered ionized and non-ionized states. Although pK_a values are generally reliable indicators of salt formation when the ΔpK_a is greater than 3, and likewise they correctly predict cocrystal formation when the ΔpK_a is negative, their predictive power is poor in the ΔpK_a range of 0 to 3. In this range, complexes between acids and bases can still form, although they can be salts or cocrystals or can contain shared protons or mixed ionization states that cannot be assigned to either category. Thus, it is not possible to designate a specific ΔpK_a value that divides the salt portion of the continuum from the cocrystal portion. The approximate transition point appears to be different for each acid/base system. For theophylline complexes, where the transition ΔpK_a ranges $0 < \Delta pK_a < 2.5$, 16 salts, two cocrystals, and two mixed ionization states were observed.

Although the distinction between salts and cocrystals can be significant from a regulatory and intellectual property perspective, it is also true that all salts and cocrystals are potentially useful from a physical property and intellectual property perspective. The debate over whether salts or cocrystals will have more useful physical properties is going to be API and project specific. In some cases a salt may be more desirable because the intrinsic solubility of a salt in water can be higher than a cocrystal because a cocrystal with

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a negative ΔpK_a, when dissolved, yields the non-ionized API whereas a salt will yield a generally more water soluble, ionized API. However, when the dissolution rate is more important than the equilibrium solubility, a cocrystal can be more advantageous than a salt form of an API. We recently demonstrated how a rapidly dissolving cocrystal of an API with low water solubility increased the bioavailability of the API significantly.[42]

In addition, in some cases the ionization state of the components may not affect the physical properties of interest. For example, in a recent study[17] that evaluated the ionization state of three API complexes, the researchers reported a salt, a structure with a shared proton, and a cocrystal of the API. All three of the structures showed improvement in solubility and bioavailability compared to the free base of the API. If physical properties are the basis for decision making concerning the utility of multicomponent solid forms of an API, then decision making based on the ionization state of the components should not be a part of the solid form selection process.

An effective approach to screening for new multicomponent crystal forms of an API is to simply remove the constraint that the counterions must have certain ΔpK_a values. By screening a wider variety of potential counterions and guest molecules (including those with negative ΔpK_a values), a screen is likely to yield a wider array of solid forms with potentially useful physical properties and valuable intellectual property. If theophylline were to be screened for new solid forms based on the prevailing approach to salt screening, ethylenediamine would not be included in a list of potential counterions and aminophylline (a successful commercial form) would not be a targeted solid form. The traditional approach of selecting counterions based on ΔpK_a would only have led to the following salts: HCl ($\Delta pK_a = 9.7$), 5-sulfosalicylic acid ($\Delta pK_a = 2.3$), and sodium hydroxide ($\Delta pK_a = 7.4$). However, more than 15 additional salts and at least 32 cocrystals of **2** are known to exist. A more comprehensive solid form screen of an ionizable API is one that also applies a crystal engineering approach focused on selecting counterions and guests based on complementary intermolecular interactions rather than just pK_a.

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Supporting Information Available: X-ray crystallographic information files (CIF) for structures **3**−**10**, tables of calculated and reported pK_a data, and IR and XRPD data for all complexes made in the course of this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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