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Cocrystal or Salt: Does It Really Matter?

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Abstract: A structural analysis of over 80 salts and cocrystals synthesized from equimolar amounts of carboxylic acids and N-heterocycles demonstrates that salt formation as a result of proton transfer from the acid to the base frequently (11/24; 45%) results in a lattice with an unpredictable chemical (solvate) or stoichiometric composition. However, if no proton transfer takes place and the result is a molecular cocrystal, a crystal lattice with an unexpected chemical content or stoichiometry is much less likely (3/61; 5%). These results indicate that the process of converting a neutral carboxylic acid into a carboxylate anion can have important structural consequences that make structure prediction and targeted supramolecular synthesis of salts much more difficult than of cocrystals. Consequently, cocrystals may offer new opportunities for producing a greater diversity of solid forms of drug substances that exhibit the appropriate balance of critical properties for development into a viable and effective drug product.

Keywords: Cocrystal; salt; hydrogen bonding; crystal lattice; crystal prediction

Active pharmaceutical ingredients (APIs) are frequently administered in the solid state as part of an approved dosage type (e.g., tablets, capsules, etc.), and solids provide a convenient and compact format to store a drug. APIs can exist in a variety of distinct solid forms, where each form may display unique physicochemical properties such as hygroscopicity, morphology, and (most importantly) solubility. Unfortunately, some potentially useful compounds with highly desirable molecular pharmacological properties may never realize their maximum potential because the physical properties of the bulk material display unfavorable bioavailability, undesirable processing characteristics, and unacceptable shelf life. How can we then alter and control solid-state properties *without* changing desirable *molecular* behavior?

Current approaches to changing properties of APIs include the utilization of ionic salts, solvates, hydrates, and polymorphs.[1] However, the design and synthesis of cocrystals have also received considerable attention partly because of fundamental interests in molecular-recognition-driven assembly processes,[2] and partly because of potential applications of cocrystals to many areas of functional solids, including pharmaceuticals.[3] Despite this flurry of activity,[4] it remains unclear if there are any good scientific reasons to suggest that cocrystals should be viewed as a distinct class of compounds compared to, for example, conventional

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(1) (a) Stahl, P. H.; Nakano, M. Pharmaceutical Aspects of the Drug Salt Form. In *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*; Stahl, P. H., Wermuth, C. G., Eds.; Wiley-VCH: New York, 2002. (b) Berge, S. M.; Bighley, L. D.; Monkhouse, D. C. Pharmaceutical salts. *J. Pharm. Sci*. **1977**, *66*, 1−19.

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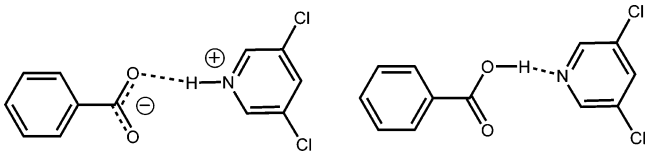
organic salts. In fact, there is considerable debate as to what actually constitutes a "cocrystal", but cocrystals are most commonly thought of as structurally homogeneous crystalline materials that contain two or more *neutral* building blocks that are present in definite stoichiometric amounts. More controversially, at times only materials that are prepared from reactants that are solids at ambient conditions are labeled "cocrystals",[5] which eliminates hydrates and other solvates, as well as compounds typically classified as clathrates or inclusion compounds. Whatever definition(s) the community finally settles on, it may be more important at this point to try to establish if cocrystals and salts display any general differences in terms of their properties, behavior, or reactivity. In this paper, we address a vital part of this issue by examining the structural consequences for solid-state assembly when proton transfer takes place between a carboxylic acid and an N-heterocycle.

Chart 1. Classification as a Salt (Left) or Cocrystal (Right) Is Determined by Proton Transfer, but Will It Have Any Significant Structural Consequences?



Many cocrystals have been prepared through strong hydrogen bonds, notably between a carboxylic acid and an N-heterocyclic hydrogen-bond acceptor.[6] However, the reaction between such components can also result in the formation of a salt if the proton is transferred from the acid to the base.[7] In principle, this event replaces the desired O−H···N interaction with a charge-assisted $O^{-}\cdots H-N^{+}$ hydrogen bond, Chart 1.

How much of an effect does this "simple" proton transfer have when it comes to preparing new molecular solids with predetermined and desirable primary intermolecular interactions and stoichiometries? Do cocrystals offer any real advantage over conventional salts in this context?

To answer the question of how proton transfer affects the reliability and predictability of intermolecular interactions within and composition of an organic molecular solid, we examined 85 crystal structures (of both cocrystals and organic salts) that were randomly selected from our pool of unpublished data produced during the last 3 years.[8] Each new compound was the result of a reaction between a carboxylic acid (aromatic and aliphatic, monoacids/diacids are included) and a wide range of N-heterocyclic rings, including pyrazole, benzimidazole, pyridine, and pyrimidine (Chart 2). Most of these organic bases contain two or more such heterocycles, and some also contain an additional hydrogen-bonding functionality such as $-C(=O)NH_2$, $-NH_2$, or $-OH$.

Many of the ligands involved in this study contain multiple N-heterocyclic rings that all act as potential hydrogen-bond

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(5) This requirement may be deemed overly restrictive, but it does offer an important distinction between solvates and cocrystals. However, in some cases, notably in the elegant work by Boese and co-workers, using low-temperature crystallizations, they intentionally prepare cocrystals with a very clear focus and deliberate strategy (see, e.g.: Kirchner, M. T.; Boese, R.; Gehrke, A.; Blaeser, D. Co-crystallization with acetylene. Part III. Molecular complexes with aromatic azacycles. *CrystEngComm* **2004**, *6*, 360).

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(8) Only crystal structures of organic compounds that were successfully solved and refined were included, and all such structures obtained for a specific time period were included in the analysis in an attempt to ensure that no bias was introduced in the selection process.

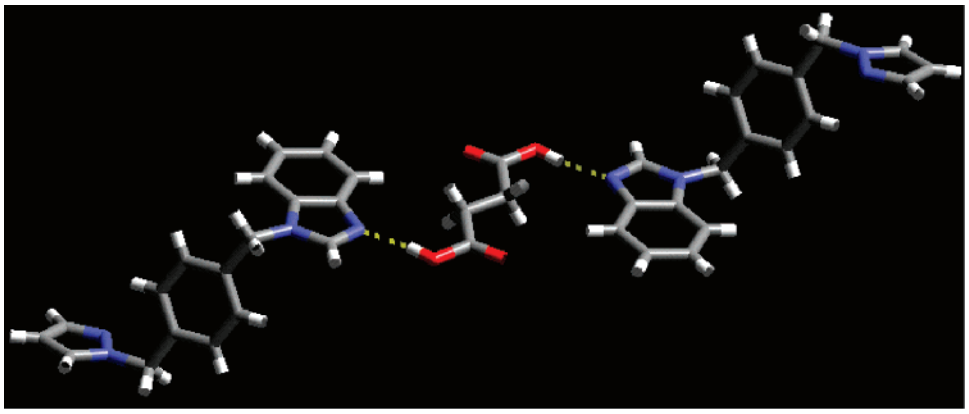
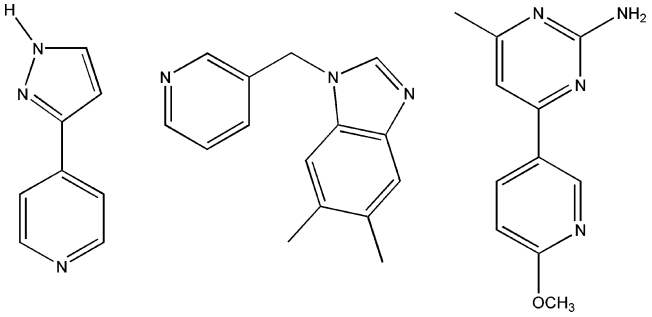


Figure 1. Example of a cocrystal, **1**, with the expected connectivity and stoichiometry.

Chart 2. Examples of Typical N-Heterocyclic Compounds Present among the 85 Structures in This Study



accepting sites. With this in mind, it is important to define what we mean by the term "expected stoichiometry" in this paper. We will complement our own structural data with information obtained from the CSD, but for the latter data points it is not always known how each compound was prepared, and it is therefore not possible to use reaction conditions/stoichiometries as a measure by which the structural outcome is judged. Instead, we will take a slightly broader view of "expected stoichiometry" based upon the number of mutually complementary hydrogen-bond donor/acceptor sites that each acid and each base offer. For example, a molecule composed of two heterocycles such as a pyridine and a pyrazole moiety can, in principle, form 1:1 or 1:2 cocrystals with monocarboxylic acids depending upon if one or both heterocycles engage in N···H−O hydrogen bonds with an acid moiety. As long as the observed primary intermolecular interactions involve an acid (or another strong hydrogen-bond donor such as an oxime) and an N-heterocycle, both a 1:1 and a 1:2 stoichiometry will be viewed as "expected" (especially in the absence of experimental data). On the other hand, if a 1:2 stoichiometry is the result of interactions that do not involve the most likely supramolecular synthons, the outcome will be classified as "unexpected".

The first part of the overall analysis of these 85 crystal structures must focus on distinguishing salts from cocrystals. In each case, the relevant proton was located from a difference Fourier map and a riding model with fixed thermal parameters ($u_{ij} = 1.2U_{ij}$(eq) for the atom to which they are bonded) was used for subsequent refinements. This information was supported by an examination of the two C−O bond lengths on the carboxylic acid (or carboxylate moiety). To summarize, the average ratio of the C−O (long) to C−O (short) bond lengths was 1.027(15) for salts and 1.081(12) for cocrystals. In addition, the endocyclic bond angles involving the most basic nitrogen atom were also examined as they can provide important information about protonated vs nonprotonated species. For example, C−N−C angles on neutral pyridine-based molecules are in the range of 117.7−118.5°, whereas the protonated analogues display bond angles over 120°.[9] Thus, by combining the structural information with suitable evidence from IR spectroscopy, all samples in this study could be unambiguously classified as either salts or cocrystals.

Out of the 85 crystal structures, 61 were cocrystals (72%) and the remaining 24 were salts (28%). Fifty-eight of the 61 cocrystals did not contain any solvates, and the stoichiometries were as expected. One example from this group is shown in Figure 1. The structure determination of 1-[(pyra-

(9) Jerzykiewicz, L. B.; Malarski, Z.; Sobczyk, L.; Lis, T.; Grech, E. The quasi-symmetric OHN and ODN bridges in the adducts of 3,5-dimethylpyridine with 3,5-dinitrobenzoic acid. *J. Mol. Struct.* **1998**, *440*, 175. Majerz, I.; Malarski, Z.; Sobczyk, L. Proton transfer and correlations between the C-O, O-H, N-H and O..N bond lengths in amine phenolates. *Chem. Phys. Lett.* **1997**, *274*, 361. Cowan, J. A.; Howard, K.; McIntyre, G. J.; Lo, S. M. F.; Williams, I. D. Variable-temperature neutron diffraction studies of the short, strong N...O hydrogen bonds in the 1:2 co-crystal of benzene-1,2,4,5-tetracarboxylic acid and 4,4′-bipyridyl. *Acta Crystallogr.* **2003**, *B59*, 794.

(10) Crystallographic data for **1**, 1-[(pyrazol-1-yl)methyl],4-[(benzimidazol-1-yl)methyl]benzene, succinic acid (2:1): $C_{40}H_{38}N_8O_4$, $M = 694.78$ amu, monoclinic, space group $P2(1)/n$, $a = 5.6367(4)$ Å, $b = 32.910(3)$ Å, $c = 9.4476(7)$ Å, $\alpha = 90°$, $\beta = 102.342(6)°$, $\gamma = 90°$, $V = 1712.0(2)$ Å^3, $Z = 2$, $D_c = 1.348$ g/cm^3, μ(Mo Kα) = 0.090 mm^{-1}, crystal size 0.45 × 0.40 × 0.04 mm^3. Data were collected at 173 K on a Bruker SMART 1000 diffractometer using Mo Kα radiation. A total of 12611 reflections ($1.24° < \theta < 28.32°$) were processed of which 4018 were unique and significant with $I > 2\sigma(I)$. Structure solution and refinement were carried out with the SHELXL-97[14] software package release 97-2. Final residuals for $I > 2\sigma(I)$ were $R_1 = 0.0545$, and $wR_2 = 0.1276$ (GOF = 0.920).

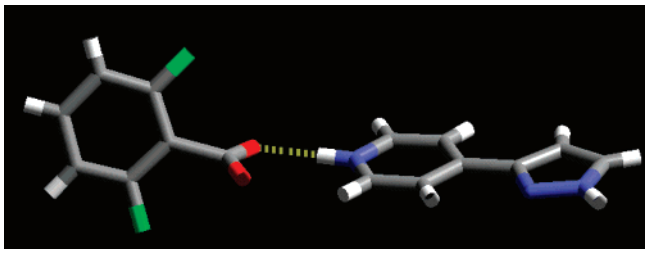


Figure 2. The primary intermolecular interaction in **2**: a pyridinium···carboxylate charge-assisted hydrogen bond.

zol-1-yl)methyl],4-[(benzimidazol-1-yl)methyl]benzene, succinic acid (2:1), **1**,[10] reveals that the diacid forms two symmetry-related O−H···N hydrogen bonds to the best acceptor on the bis-N-heterocycle. The benzimidazole moiety is more basic than the pyrazole ring and is therefore more competitive for the hydrogen-bond donor.

In three of the cocrystals (4.9%) a solvent molecule was incorporated into the lattice (ethanol or water).

Twenty-four of the 85 structures were found to be salts, resulting from a proton transfer from the acid to a nitrogen atom in an N-heterocycle. Thirteen of these 24 compounds displayed the expected stoichiometry and primary intermolecular interaction; a charge-assisted $O^-\cdots H-N^+$ interaction had simply replaced the O−H···N hydrogen bond without any dramatic structural consequences. One such example is given in Figure 2. The structure determination of 3-(4-pyridyl)pyrazole, 2,6-difluorobenzoic acid (1:1), **2**,[11] shows that the pyridine moiety (which is more basic than the pyrazole site) has been protonated, resulting in a carboxylate··· pyridinium intermolecular interaction.

Two of the 24 salts (8.3%) were solvates (ethanol), and nine out of the 24 salts (37.5%) displayed an unpredictable

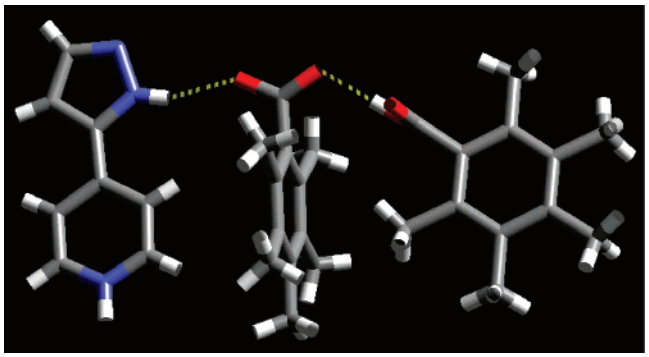


Figure 3. The environment around the carboxylate moiety in **3**.

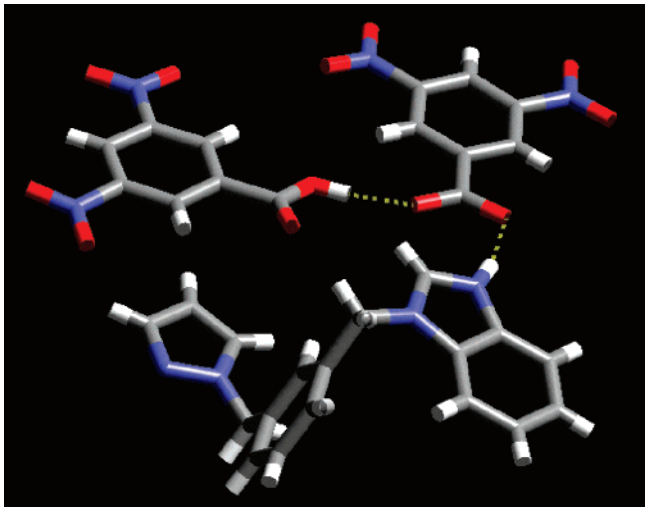


Figure 4. Proton transfer to the benzimidazole of **4** brings in a "free" acid.

stoichiometry resulting from the incorporation of a "free" carboxylic acid into the lattice. The presence of a carboxylic acid moiety is both unpredictable and highly disruptive as shown in the structure determinations of 3-(4-pyridinium)-pyrazole pentamethylbenzoate pentamethylbenzoic acid (1:1:1), **3**,[12] and 1-[(pyrazol-1-yl)methyl], 3-[(benzimidazol-1-yl)methyl]benzene, 3,5-dinitrobenzoate, 3,5-dinitrobenzoic acid (1:1:1), **4**,[13] and makes it impossible to establish a reliable a priori estimate of the primary intermolecular interactions and connectivities, Figures 3 and 4.

(11) Crystallographic data for **2**, 3-(4-pyridyl)pyrazole, 2,6-difluorobenzoic acid (1:1): $C_{15}H_{11}F_2N_3O_2$, M = 303.27 amu, monoclinic, space group $P2(1)/n$, a = 7.1555(8) Å, b = 17.958(2) Å, c = 10.9686(12) Å, α = 90°, β = 101.301(2)°, γ = 90°, V = 1382.1(3) Å^3, Z = 4, D_c = 1.457 g/cm^3, μ(Mo Kα) = 0.118 mm^{-1}, crystal size 0.46 × 0.16 × 0.07 mm^3. Data were collected at 203 K on a Bruker SMART 1000 diffractometer using Mo Kα radiation. A total of 5396 reflections (2.21° < θ < 28.24°) were processed of which 3167 were unique and significant with $I > 2\sigma(I)$. Structure solution and refinement were carried out with the SHELXL-9714 software package release 97-2. Final residuals for $I > 2\sigma(I)$ were R_1 = 0.0453, and wR_2 = 0.1056 (GOF = 1.050).

(12) Crystallographic data for **3**, 3-(4-pyridinium)pyrazole pentamethylbenzoate pentamethylbenzoic acid (1:1:1): $C_{32}H_{39}N_3O_4$, M = 529.66 amu, triclinic, space group $P\bar{1}$, a = 8.8864(5) Å, b = 11.9875(7) Å, c = 13.7015(8) Å, α = 99.3800(10)°, β = 93.1910(10)°, γ = 107.5560(10)°, V = 1364.42(14) Å^3, Z = 2, D_c = 1.289 g/cm^3, μ(Mo Kα) = 0.085 mm^{-1}, crystal size 0.09 × 0.24 × 0.36 mm^3. Data were collected at 100 K on a Bruker SMART 1000 diffractometer using Mo Kα radiation. A total of 16736 reflections (2.53° < θ < 30.53°) were processed of which 8185 were unique and significant with $I > 2\sigma(I)$. Structure solution and refinement were carried out with the SHELXL-97[14] software package release 97-2. Final residuals for $I > 2\sigma(I)$ were R_1 = 0.0529, and wR_2 = 0.1240 (GOF = 0.947).

(13) Crystallographic data for **4**, 1-[(pyrazol-1-yl)methyl], 3-[(benzimidazol-1-yl)methyl]benzene, 3,5-dinitrobenzoate, 3,5-dinitrobenzoic acid (1:1:1): $C_{32}H_{24}N_8O_{12}$, M = 712.59 amu, triclinic, space group $P\bar{1}$, a = 9.7657(6) Å, b = 11.7691(7) Å, c = 14.0803(9) Å, α = 86.2270(10)°, β = 74.1630(10)°, γ = 86.2020(10)°, V = 1551.53(17) Å^3, Z = 2, D_c = 1.525 g/cm^3, μ(Mo Kα) = 0.120 mm^{-1}, crystal size 0.46 × 0.36 × 0.28 mm^3. Data were collected at 100 K on a Bruker SMART 1000 diffractometer using Mo Kα radiation. A total of 12611 reflections (2.24° < θ < 30.08°) were processed of which 4018 were unique and significant with $I > 2\sigma(I)$. Structure solution and refinement were carried out with the SHELXL-97[14] software package release 97-2. Final residuals for $I > 2\sigma(I)$ were R_1 = 0.0513, and wR_2 = 0.1240 (GOF = 1.024).

Table 1. Hydrogen-Bond Geometries for **1**−**4**

	donor-H···acceptor[a]	D−H	H···A	D···A	D−H···A
1	O41.H41···N13	0.933(11)	1.711(12)	2.6291(11)	167.1(11)
2	N11−H11···O31	0.95(2)	1.68(2)	2.6292(18)	178.6(19)
	N21−H21···O31*	0.92(2)	1.85(2)	2.7684(19)	177.7(18)
3	N12−H12···O41	0.908(17)	1.908(17)	2.7732(16)	158.7(15)
	O61−H61···O42	0.899(18)	1.690(18)	2.5769(14)	168.4(16)
	N21−H21···O41**	0.989(16)	1.682(17)	2.6545(15)	167.0(14)
4	N13−H13···O51	0.935(15)	1.764(15)	2.6862(12)	168.0(14)
	O41−H41···O52	0.921(18)	1.602(18)	2.5207(12)	175.2(16)

[a] Operators for generating equivalent atoms: * *x*, *y*, 1 + *z*, ** *x* − 1, *y*, *z*.

Table 2. Lattice Contents in 64 Cocrystals and 21 Salts

	cocrystals, %	salts, %
solvates	4.9	8.3
unexpected stoichiometry of the two reactants	0	37.5
unexpected lattice composition (total)	4.9	45.8

A summary of all relevant hydrogen-bond geometries for **1**−**4** is given in Table 1.

The results of the structural analysis of 85 crystal structures (61 cocrystals and 24 salts) are summarized in Table 2.

Based on this study, it is apparent that the formation of salts tends to wreak havoc when attempting to combine two or more solids into the same crystalline lattice in a reliable and predictable manner. There is undoubtedly a dramatic difference in structural behavior between the two classes of compounds at least when comparing cocrystals of carboxylic acids and carboxylate salts. An explanation for this could be that a carboxylate moiety is not readily satisfied by a single hydrogen-bond donor which, in effect, makes it necessary to bring in a "free" carboxylic acid, whereas the charge distribution around the oxygen atoms in a neutral carboxylic acid makes it a less powerful or demanding hydrogen-bond acceptor site.

It is quite likely that it would be possible to convert some of these cocrystals into salts (and vice versa), but we have not attempted to induce or force proton transfer in all cocrystals by changing reaction conditions. Mootz et al.[14] found that a 1:1 mixture of pyridine and formic acid resulted in the formation of a neutral cocrystal assembled via the expected O−H···N hydrogen bond. However, changing the ratio to 1:4 (pyridine to formic acid) did lead to proton transfer, and interestingly enough, the resulting lattice was composed of a pyridinium cation, a formate anion, and three additional formic acid molecules. In the experiments presented herein, the reactants were always combined in stoichiometric amounts and all reactions were carried out in similar solvents (mostly methanol/ethanol). Therefore, the phenomenon of proton transfer as a function of the ratio of acid to ligand is not likely to influence the observed structural trends and the subsequent interpretations.

(14) Wiechert, D.; Mootz, D. Molecular beside ionic: crystal structures of a 1/1 and a 1/4 adduct of pyridine and formic acid. *Angew. Chem., Int. Ed.* **1999**, *38*, 1974.

Table 3. Lattice Contents in Ca. 100 Cocrystals and 130 Salts Obtained from the CSD

	cocrystals, %	salts, %
solvates	5	19
unexpected stoichiometry of the two reactants	1	14
unexpected lattice composition (total)	6	33

Table 4. Lattice Contents in Ca. 75 Cocrystals and 100 Salts Obtained from the CSD (Compounds with $-NH_2$ Groups Excluded)

	cocrystals, %	salts, %
solvates	7	23
unexpected stoichiometry of the two reactants	1	17
unexpected lattice composition (total)	8	40

One can also argue that the exact classification of a compound as a salt or a cocrystal can at times be somewhat ambiguous. For example, Nygren et al.[15] used X-ray and neutron diffraction to study hydrogen bonding between urotropine *N*-oxide and formic acid as a function of temperature. The exact location of the proton was found to change with temperature, and under certain conditions the system could be described as displaying partial proton transfer from the acid to the *N*-oxide moiety. In this study, X-ray diffraction for all 85 crystal structures was collected close to 100 K and no attempt was made to determine if a cocrystal would be better described as a salt at other temperatures, and it is therefore it is unlikely that any unwanted bias, in terms of classification, has found its way into this systematic structural analysis.

In order to reduce or eliminate any systematic errors that may have been present in our study as a result of a bias in the type of compounds and chemical functionalities that we have examined, we also decided to complement our data with relevant information on salts and cocrystals obtained from the Cambridge Structural Database (Version 5.27).[16]

We included only pyridine/benzoic acid and pyridinium/benzoate fragments as they represent a significant group of acid−base based salts/cocrystals and we were able to extract over 100 hits for each class. The analysis of the lattice content was carried out as described previously for our own compounds, and the results are shown in Table 3.

Although the disparity in behavior between cocrystals and salts is not quite as dramatic in the structures from CSD as it is in our own group, there is no doubt that the trends and patterns of behavior are significantly different.

In order to find out if the presence/absence of chemical moieties such as $-NH_2$ groups could alter the outcome, we

(15) Nygren, C. L.; Wilson, C. C.; Turner, J. F. C. Electron and Nuclear Positions in the Short Hydrogen Bond in Urotropine-*N*-oxide·Formic Acid. *J. Phys. Chem. A* **2005**, *109*, 1911.

(16) Allen, F. A.; The Cambridge Structural Database: a quarter of a million crystal structures and rising, *Acta Crystallogr. B* **2002**, *58*, 380.

repeated the search listed in Table 3, but this time all structures that contained amino groups were excluded, Table 4.

Although we may need a more extensive and detailed survey of published structures, the trend so far indicates that the absence of an $-NH_2$ group will make unexpected lattice compositions of salts even more likely, because such a group is capable of compensating for the extra demand for hydrogen-bond donors that a carboxylate moiety brings forth.

Finally, based upon the type of compounds that were included in this study (and supported by existing structural data from the CSD), it seems that if we want to improve our chances of preparing a heteromeric organic solid without unexpected stoichiometries or unwanted solvates/hydrates (with a view to improving/controlling certain physical properties), then the answer to the question posed in the title is undoubtedly: Yes! These results may be very significant when it comes to demonstrating the advantage of cocrystals in a variety of pharmaceutical formulations, and they may also have considerable ramifications for patent processes. We are currently exploring the generality of our observations through further database studies of other families of compounds.

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Supporting Information Available: Crystallographic information (.cif) and a table of crystallographic data for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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