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ARTICLE

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An Investigation of the Hydrogen-Bond Preferences and Co-crystallization Behavior of Three Didonor Compounds.

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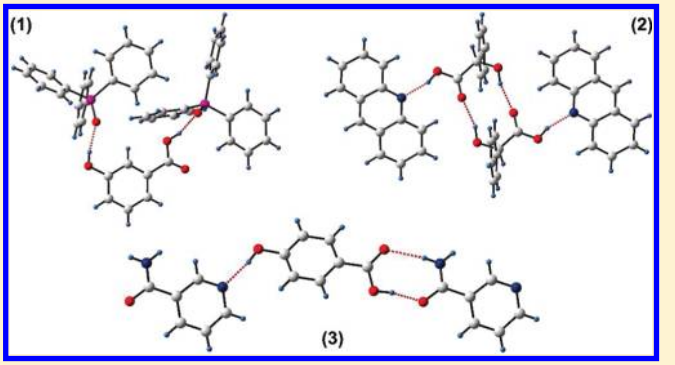
Supporting Information

ABSTRACT: We assess the suitability of the three didonor compounds as building blocks for ternary co-crystals of the type (didonor)(monoacceptor)$_2$. A Cambridge Structural Database (CSD) survey was carried out to analyze the hydrogen-bond connectivity and develop a strategy for the preparation of the desired co-crystal. Six specific compounds were selected and crystals were grown from 1:1 and 1:2 solutions of didonor compounds (*m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, and racemic mandelic acid) and acceptor compounds (acridine, triphenylphosphine oxide, and nicotinamide) leading to three co-crystals (*m*-hydroxybenzoic acid)·(triphenylphosphine oxide)$_2$ (**1**), ((*RS*)-mandelic acid)·(acridine) (**2**) and (*p*-hydroxybenzoic acid)·(nicotinamide) (**3**). Characterization by single-crystal structure determination confirms the success of this design strategy.

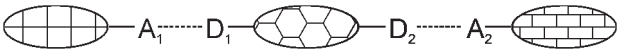


INTRODUCTION

When it comes to planning the supramolecular synthesis of neutral multicomponent molecular complexes, the supramolecular chemist must consider the entire hydrogen-bonding functionality of the molecules under investigation.[1] Classical hydrogen bonds which include O−H···O, O−H···N, N−H···O, and N−H···N,[2] are the likely candidates to be used in such a synthesis and most likely to succeed.[3] For example, a recent analysis of the CSD[4] showed that hydroxyl groups (found in alcohols, phenols, and carboxylic acids) hydrogen bond to aromatic nitrogen and primary amide acceptors with extremely high frequency. These hydrogen bonds have been recognized as robust supramolecular heterosynthons suitable for co-crystal synthesis.[4] In addition, it has been found that heteromeric interactions, those between different functional groups, are more likely to occur than between the same functional group (homomeric interactions).[5]

A large number of co-crystals take advantage of the strong hydrogen-bond attraction between a hydroxyl group donor (alcohols, phenols, and carboxylic acids) and a strong hydrogen-bond acceptor such as a phosphine oxide, pyridine, or amide.[6] Our ultimate goal is to take advantage of these reliable functional group attractions in designing ternary co-crystals (containing 3 different compounds in the same crystal). Aakeröy and co-workers[7a] have published several examples of ternary co-crystals in recent years where a diacceptor compound having two chemically different acceptors is crystallized with two different carboxylic acids. Our strategy here is to crystallize a didonor compound having two chemically different hydroxyl groups with two chemically different acceptor compounds, each appended with one of the strong acceptors listed above. If each of the two different donors preferentially hydrogen bonds to one of the two different acceptors, a ternary complex would form. Under favorable solubility conditions, this complex would precipitate as a ternary co-crystal (Scheme 1). Ideally, we would be able to select a set of two donors and two acceptors that would pair up in a predictable manner when appended to molecules as shown in Scheme 1.

Scheme 1. Prototypical Schematic Ternary Co-crystal, Where D Represents a Hydrogen-Bond Donating Group and A Represents an Accepting Group



Here we describe our investigation of the hydrogen-bond behavior of a set of three functional groups known for their donating behavior and three functional groups known for their accepting behavior in the context of a limited set of molecules. We investigate the crystallization behavior of binary solutions

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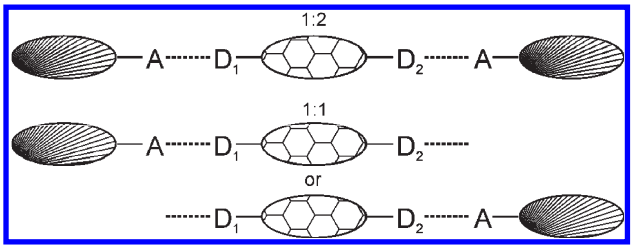
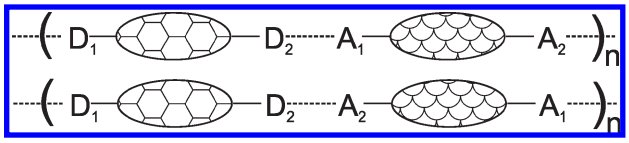
Scheme 2. Possible Stoichiometric Variants of Binary Didonor/Monoacceptor Co-crystals



Scheme 3. Competition between Two Donor and Two Acceptor Groups in Binary Didonor/Diacceptor Co-crystals



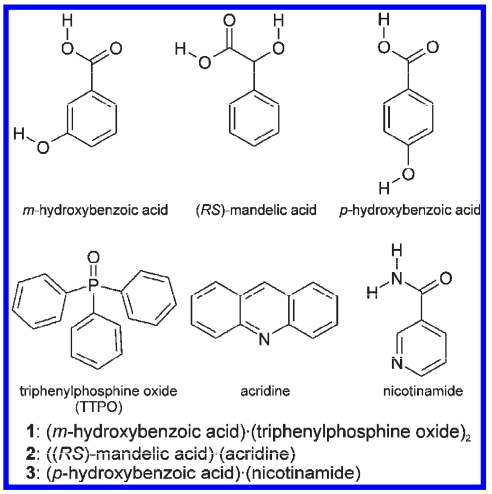
containing a didonor compound and a strong acceptor compound. For this work we selected three didonor compounds, each containing a carboxylic acid as the first donor. Two of these compounds (*m*-hydroxybenzoic acid and *p*-hydroxybenzoic acid) contain a phenol as the second donor, while the third compound (*RS*)-mandelic acid contains an alcohol as the second donor group. These didonor compounds were co-crystallized with compounds selected for their known accepting ability: triphenylphosphine oxide (with a single phosphine oxide acceptor), acridine (with a single-pyridine acceptor), and nicotinamide (with both a pyridine and an amide carbonyl acceptor). Although the primary amide also acts as a donor, its principal role in these structures is that of an acceptor and we will refer to it here as a hydrogen-bond acceptor.

A binary co-crystal containing a didonor molecule and a monoacceptor molecule (such as triphenylphosphine oxide or acridine) would be expected to show one of the three connectivity patterns illustrated in Scheme 2. Preferential hydrogen-bonding of both donors to the monoacceptor molecule would result in a 1:2 co-crystal with the connectivity shown. Preferential hydrogen-bonding of only one of the two donors to the monoacceptor molecule would result in a 1:1 co-crystal displaying one of the two connectivity patterns shown in Scheme 2, where the remaining donor hydrogen bonds to a neighboring didonor molecule. In addition, one might be able to exert a level of control on the final co-crystal stoichiometry simply by adjusting the mole ratio of the components in the crystallizing solution.

Alternatively, one can study the hydrogen-bond preferences of a didonor compound by co-crystallizing it with a diacceptor compound where A_1 and A_2 are chemically different acceptor groups (such as nicotinamide) setting up a competition between two donors and two acceptors. The preference of one of the two 1:1 co-crystal patterns shown in Scheme 3 would provide insight into the hydrogen-bond preferences of the groups involved.

In this study, we co-crystallized didonors both with monoacceptor and diacceptor compounds and report three new co-crystals resulting from the six compounds listed above: (*m*-hydroxybenzoic acid)·(triphenylphosphine oxide)$_2$ (**1**), ((*RS*)-mandelic acid)·(acridine) (**2**) and (*p*-hydroxybenzoic acid)·(nicotinamide) (**3**). The hydrogen-bonding interactions observed in these three co-crystals are compared to those observed in other co-crystals involving the same compounds deposited in the Cambridge Structural Database (CSD). Trends in hydrogen-bond behavior of these six compounds are sought.

Chart 1. Six Neutral Molecules Investigated in This Report and Their Three Co-crystals (1−3)



EXPERIMENTAL SECTION

Materials. *m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, (*RS*)-mandelic acid, triphenylphosphine oxide, acridine and nicotinamide were purchased from commercial sources (Aldrich) and used without further purification. All solvents used in the study were of AR (99.9%) quality.

Co-crystal 1 (1:2 *m*-Hydroxybenzoic acid/Triphenylphosphine Oxide). A 1:2 stoichiometric amount of *m*-hydroxybenzoic acid (55 mg, 0.40 mmol) and triphenyphosphine oxide (224 mg, 0.80 mmol) was dissolved in 13 mL of toluene. Colorless prisms were obtained upon slow evaporation of the solution at room temperature. Identical 1:2 co-crystals (by FTIR, KBr pellet) were obtained from 1:1 and from 1:2 solutions of 20% acetone/80% toluene.

Co-crystal 2 (1:1 (*RS*)-Mandelic acid/Acridine). A 1:1 stoichiometric amount of (*RS*)-mandelic acid (61 mg, 0.40 mmol) and acridine (72 mg, 0.40 mmol) was dissolved in 9 mL of 33% acetone/67% cyclohexane. Greenish yellow prisms were obtained upon slow evaporation of the solution at room temperature. Identical 1:1 co-crystals (by FTIR, KBr pellet) were obtained from a 1:2 solution of 33% acetone/67% cyclohexane.

Co-crystal 3 (1:1 *p*-Hydroxybenzoic Acid/Nicotinamide). A 1:1 stoichiometric amount of *p*-hydroxybenzoic acid (100 mg, 0.819 mmol) and nicotinamide (113 mg, 0.819 mmol) was dissolved in 5 mL of methanol and colorless crystals grown by slow evaporation over a few days at room temperature.

Table 1 summarizes the results obtained from the full set of co-crystallization experiments (co-crystal stoichiometries reported with didonor compound listed first.) Asterisks denote that the single-crystal structure has been determined and is being submitted for publication elsewhere. Stoichiometries of co-crystals without X-ray structures were determined by proton NMR.

Single-Crystal X-ray Diffraction (SCXRD). Intensity data were collected on a Bruker SMART 1K CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA) and performed at T = 293 K. The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program SAINT+,[8] and empirical absorption corrections were made using the program

Table 1. Summary of All Didonor/Acceptor Co-crystallization Results

	m-hydroxybenzoic acid	(*RS*)-mandelic acid	*p*-hydroxybenzoic acid
TPPO	co-crystal **1** (1:2)	oil (no crystals)	crystals from oil (identity uncertain)
acridine	1:1(2 forms)*, 1:2*, 3:2, 1:4.5 hemihydrate	co-crystal **2** (1:1)	1:1
nicotinamide	XAQQIQ[5f]	JILZOU[3b] with (*R*)-mandelic acid	co-crystal **3** (1:1)

Table 2. Crystallographic Data for 1−3

	1	**2**	**3**
formula	$C_{43}H_{36}O_5P_2$	$C_{21}H_{17}NO_3$	$C_{13}H_{12}N_2O_4$
mw	694.66	331.36	260.25
T (K)	293(2)	293(2)	293(2)
cryst size (mm^3)	0.20 × 0.20 × 0.20	0.30 × 0.20 × 0.20	0.40 × 0.10 × 0.06
cryst syst	monoclinic	monoclinic	monoclinic
space group (No.)	$P2_1/n$ (14)	$P2_1/c$ (14)	$C2/c$ (15)
a (Å)	11.600(1)	10.320(3)	30.962(4)
b (Å)	13.569(1)	21.133(7)	7.371(1)
c (Å)	23.303(2)	7.825(3)	11.223(2)
β (deg)	90.567(2)	102.105(6)	107.777(6)
V ($Å^3$)	3667.7(6)	1668.5(9)	2438.8(5)
Z	4	4	8
ρ(calcd) ($Mg\ m^{-3}$)	1.258	1.319	1.418
μ(Mo−K_α) (mm^{-1})	0.164	0.089	0.107
theta range for data collection (deg)	1.74 to 25.50	1.93 to 25.49	2.76 to 25.50
no. of reflns collected	17873	9017	6314
no. of unique data [R(int)]	6823 [0.0784]	3096 [0.0391]	2263 [0.0271]
data with $I > 2\sigma(I)$	2938	1837	1614
final R ($I > 2\sigma(I)$)	0.0483	0.0488	0.0412
final *wR2* (all data)	0.1579	0.1554	0.1307
CCDC No.	812396	812397	812398

SADABS.[8] The crystal structures were solved in the WinGX[9] suite of programs by direct methods using by direct methods using SHELXS-97.[10] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using SHELXL-97.[10] Thereafter, all hydrogen atoms attached to N and O atoms were located in the difference fourier map and their coordinates refined freely with isotropic parameters 1.5 times (O) or 1.2 times (N) those of the heavy atoms to which they are attached. All C-H hydrogen atoms were placed at idealized positions and refined as riding atoms with isotropic parameters 1.2 times those of the heavy atoms to which they are attached. Diagrams and publication material were generated using ORTEP-3,[11] PLATON,[12] and DIAMOND.[13] Further crystallographic data are summarized in Table 2.

Cambridge Structural Database. All searches were done on the version 5.31 Database with the November 2009 and February 2010 updates.[14] The filters applied to all searches are: 3D coordinates determined, R-factor ≤0.075, not disordered, no errors, no ions, no powder structures, only organics. The searches were performed with the six molecules as the target molecule as a query. The search for *m*-hydroxybenzoic co-crystals gave 13 hits, which was reduced to 11 after removing the crystal structures of the search compound. The search for *p*-hydroxybenzoic co-crystals gave 27 hits, which were reduced to 16 after removing duplicate entries, hydrates and any molecular salt structures. The search for nicotinamide co-crystals gave 22 hits, which was reduced to 11 after removing crystal structures of the target molecule, host−guest complexes and compounds with covalent bonds to the pyridine. The search for mandelic acid gave 21 hits, which were reduced to 5 hits by removing molecular salts, structures of the target molecule, clathrates and hydrates. The search for triphenylphosphine oxide co-crystals gave 88 hits, which were reduced to 45 by removing crystal structures of the target compound, hydrates, structures with bonds to metals, structures with halogen bonding or C−H···X hydrogen bonding only, duplicates, and complexes with inorganic acids. The search for acridine co-crystals gave 26 hits, which were reduced to 16 by removing the structures of the parent compound, and those that do not form any strong hydrogen bonds (halogen bonding, C−H···X are excluded).

RESULTS

The crystal structure of **1** has one molecule of *m*-hydroxybenzoic acid and two molecules of triphenylphosphine oxide (**TPPO**) in the asymmetric unit (Figure 1). The carboxylic acid and phenol protons both hydrogen bond to the phosphine oxide of the TPPO molecules to form a trimeric supermolecule through O−H···O hydrogen bonds (Figure 2a). The trimeric supermolecules pack in ribbons along [101] and are connected by four C−H···O interactions between the aromatic rings of the TPPO and the O atoms of *m*-hydroxybenzoic acid and TPPO (Figure 2b). Table 3 summarizes the hydrogen-bond geometries.

The crystal structure of **2** has one molecule each of mandelic acid and acridine in the asymmetric unit (Figure 1). Two mandelic acid molecules are connected into a dimer by a $R_2^2(10)$ ring formed by a O−H···O hydrogen bond from the alcohol O3 to the carbonyl O2 (Figure 3a). The dimer hydrogen

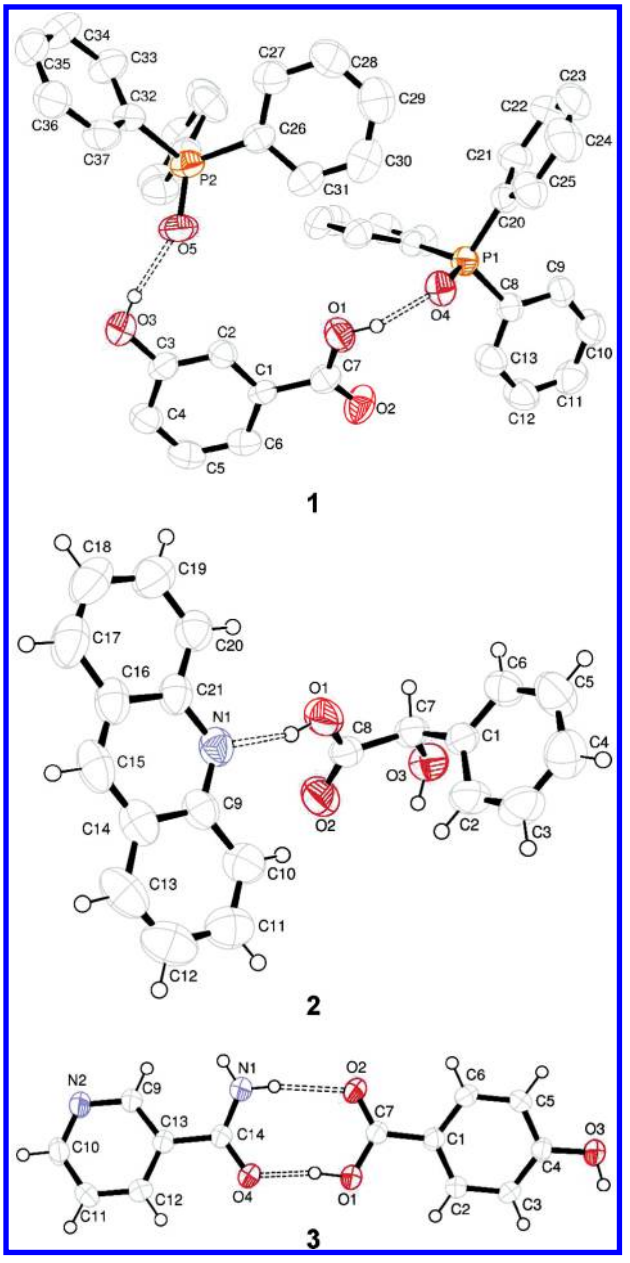


Figure 1. Asymmetric unit and atomic numbering scheme of co-crystals **1**−**3**, and 50% displacement ellipsoids. Only the symmetry independent hydrogen bonds are shown. For clarity, the H atoms not involved in hydrogen bonding are omitted in **1**.

bonds to two acridine molecules through the carboxylic acid proton to the pyridine N. This forms a four-membered supermolecule. The crystal packing has alternating layers of mandelic acid and acridine along the *b*-axis such that the acridine molecules of adjacent interdigitated interdigitated and feature $\pi\cdots\pi$ interactions between them ($C_g\cdots C_g$ distance: 3.897(8) Å) (Figure 3b). Table 3 summarizes the hydrogen-bond geometries.

The crystal structure of co-crystal **3** has one molecule each of *p*-hydroxybenzoic acid and nicotinamide in the asymmetric unit. The *p*-hydroxybenzoic acid and nicotinamide molecules hydrogen bond using four N−H···O and two O−H···O hydrogen bonds. The carboxylic acid and the amide groups hydrogen bond to each other forming $R_2^2(8)$ rings. Pairs of neighboring rings

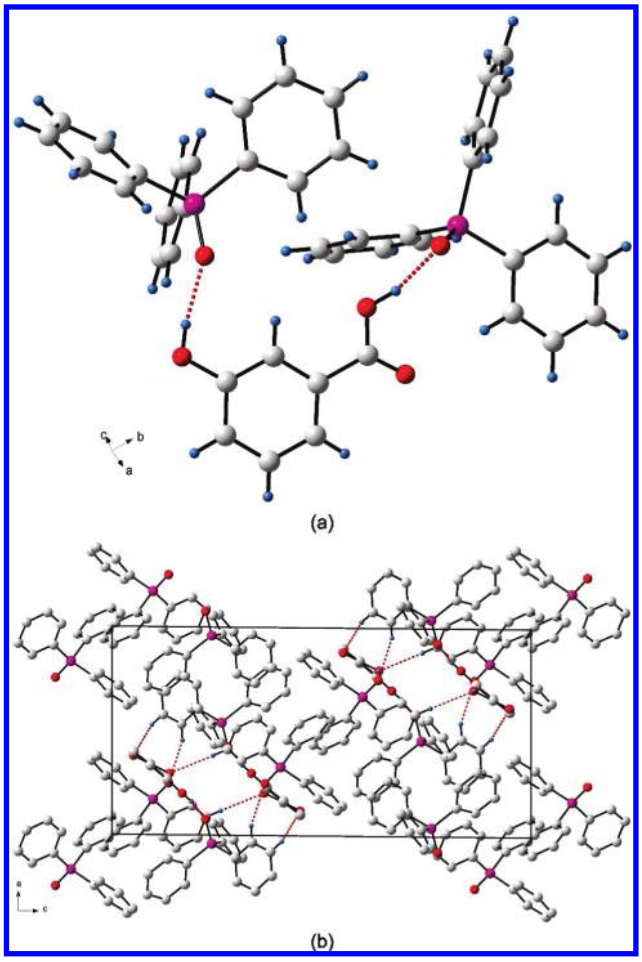


Figure 2. (a) Two hydrogen-bonding interactions in co-crystal **1** form a three-membered supermolecule. (b) Packing of the supermolecules, showing the C−H···O interactions.

$R_2^2(8)$ are connected through N−H···O hydrogen bonding forming a $R_4^2(8)$ring. The phenol proton hydrogen bonds to the pyridine N atom to form infinite ribbons along $[\bar{1}01]$ (Figure 4a). The ribbons layer above each other along the *b*-axis (Figure 4b). Table 3 summarizes the individual hydrogen-bond geometries.

DISCUSSION

Here we present three examples of didonor co-crystals, each having a preferred stoichiometry that is independent of the solution stoichiometry. Two of the co-crystal pairs we have chosen show a preference for 1:1 co-crystal formation, while one shows a preference for 1:2 co-crystal formation. Individual CSD searches for co-crystals involving each of the six molecules show how often a particular type of heteromeric or homomeric interaction is observed in the total number of co-crystals (Table 4). The hydrogen-bonding contact criteria were the default values used in MERCURY[15] and short contacts were also included by inspection if hydrogen-bond donors appeared not to be used. All interactions were catalogued.

1:2 *m*-Hydroxybenzoic Acid/Triphenylphosphine Oxide Co-crystal 1. Co-crystal **1**, in which both the carboxylic acid and phenol groups of *m*-hydroxybenzoic acid form hydrogen bonds with two independent TPPO molecules, provides an example of the 1:2 co-crystal represented in Scheme 2. This

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Table 3. Geometrical Parameters for Hydrogen Bonds in 1−3

compd[a]	d(D−H) (Å)	d(H···A) (Å)	d(D···A) (Å)	∠(D−H···A) (deg)
1				
O1−H1···O4	0.87(4)	1.73	2.571(3)	162(4)
O3−H3···O5	0.84(4)	1.85(4)	2.679(3)	167(5)
C24−H24···O1^{i}	0.93	2.69	3.616(5)	177
C36−H36···O2^{ii}	0.93	2.51	3.400(5)	160
C37−H37···O4^{ii}	0.93	2.52	3.378(4)	153
C41−H41···O2^{iii}	0.93	2.50	3.350(5)	153
2				
O1−H1···N1	0.82	1.79	2.573(2)	160
O3−H3···O2^{iii}	0.93(3)	1.94(3)	2.839(3)	162(3)
C4−H4···O3^{iv}	0.93	2.63	3.372(4)	138
C6−H6···O1^{v}	0.93	2.61	3.355(3)	138
3				
O1−H1···O4	0.95(3)	1.67(30	2.617(2)	169(3)
O3−H3···N2^{vi}	0.89(3)	1.87(3)	2.743(2)	168(2)
N1−H1S···O2	0.85(3)	2.08(4)	2.924(2)	172(3)
N1−H1A···O2^{vii}	0.86(3)	2.16(4)	2.965(2)	155(3)

[a] Symmetry transformation codes: (i) $-x+3/2, y+1/2, -z+3/2$; (ii) $-x+3/2, y-1/2, -z+3/2$; (iii) $-x+1, -y+1, -z+1$; (iv) $x, y, z+1$; (v) $-x, -y+1, -z+1$; (vi) $x+1/2, -y+1/2, z+1/2$; (vii) $-x+1, y, -z+3/2$.

1:2 co-crystal forms by slow evaporation of 1:1 as well as 1:2 solutions of the reactants. We searched the CSD beforehand to gain insight into the hydrogen-bonding behavior of the two starting materials. We found 11 *m*-hydroxybenzoic acid co-crystal structures in the CSD (reduced set) yielding 12 symmetry independent *m*-hydroxybenzoic acid molecules. In 9 of the 12, both the carboxyl proton and the phenol proton of *m*-hydroxybenzoic acid hydrogen bonds to crystallographically independent acceptor molecules. In one structure, only the carboxyl proton hydrogen bonds to the acceptor molecule and in another, only the phenol donates to the acceptor molecule. In short, there is no clear dominance of the carboxyl proton or the phenolic proton of *m*-hydroxybenzoic acid in binding to the acceptor compound. The most prevalent hydrogen bond is a carboxyl to aromatic nitrogen appearing 9 times in the 11 structures. It is closely followed by the phenol to aromatic nitrogen hydrogen bond which appears seven times. The same set of structures includes 14 symmetry independent acceptor molecules, eleven which act as diacceptors (accepting twice from a donor molecule) and only three which act as monoacceptors. One of those three, HONTOU, (which the acceptor compound is 4-phenylpyridine) provides the only example in the database of *m*-hydroxybenzoic acid displaying the 1:2 pattern shown in Scheme 2. Our own 1:2 *m*-hydroxybenzoic acid/acridine co-crystal also displays this pattern. The second monoacceptor structure, SUVZEO, forms a 1:1 co-crystal of the type displayed in Scheme 2. The phenol hydrogen bonds to the N-oxide acceptor while the carboxylic acids bond to each other in an $R_2^2(8)$ dimer. The third structure containing monoaccepting molecules, HONVIQ, is a 3:2 co-crystal with an ADADA pattern in which the terminal molecules accept only once (even though they have two terminal nitrogens), whereas the central molecule accepts twice. Eight of the 11 structures that have diacceptor compounds display 1:1 hydrogen-bond patterns with alternating didonor and diacceptor molecules of the type represented in Scheme 3. Only three of the diacceptor compounds in these structures were asymmetrical (nicotinamide, isonicotinamide, and caffeine), differentiating between the two acceptors. Co-crystals with such compounds could potentially provide valuable insight into the hydrogen-bond preferences of the donor/acceptor set. All three of these examples have an amide carbonyl and an aromatic nitrogen. In both the isonicotinamide and caffeine structures, the phenol hydrogen bonds to the amide while the carboxylic acid hydrogen bonds to the aromatic nitrogen. In nicotinamide, the opposite happens: the carboxylic acid forms a $R_2^2(8)$ ring with the amide while the phenol hydrogen bonds to the aromatic nitrogen. While this set of asymmetric *m*-hydroxybenzoic acid/diacceptor structures is much too small to draw any conclusions about the hydrogen-bond preferences of the carboxyl and phenolic protons of 3HBA, it clearly shows that on this particular didonor compound, the pairing between the two donors and two acceptors can go either way. Interestingly, in the *m*-hydroxybenzoic acid/pyrazine co-crystal, both of the equivalent aromatic nitrogens accept from carboxylic acids while the phenols are left to hydrogen bond to the acid carbonyl. This results in an unpredicted 2:1 pattern where two didonor molecules alternate with one diacceptor molecule in an infinite $(DDA)_n$ chain.

As shown by our CSD search, TPPO has a rich history of co-crystal formation (45), especially with carboxylic acid (17) or phenol/alcohol donors (13/4). This could be due to the weak hydrogen bonding interactions that TPPO can undergo with itself, and hence can be used to obtain co-crystals with a compound that has been difficult to crystallize.[16] The four polymorphs of TPPO[17] all have weak C−H···O=P hydrogen bonding, and hence molecules with strong donor functionalities will hydrogen bond to the O=P group preferentially and will not have to compete much with a C−H donor.[16]

1:1 Mandelic Acid/Acridine Co-crystal 2. Mandelic acid, which has both acid and alcohol donor groups, uses the COOH···N heteromeric interaction from the acid to the pyridine N atom of acridine to form co-crystal **2** with acridine; whereas the alcohol hydrogen bonds to the carbonyl of the acid functional group forming an $R_2^2(10)$ hydrogen-bonded ring. This preference is somewhat surprising especially when one considers that this same 1:1 co-crystal forms in a 1:2 solution having a 2-fold excess

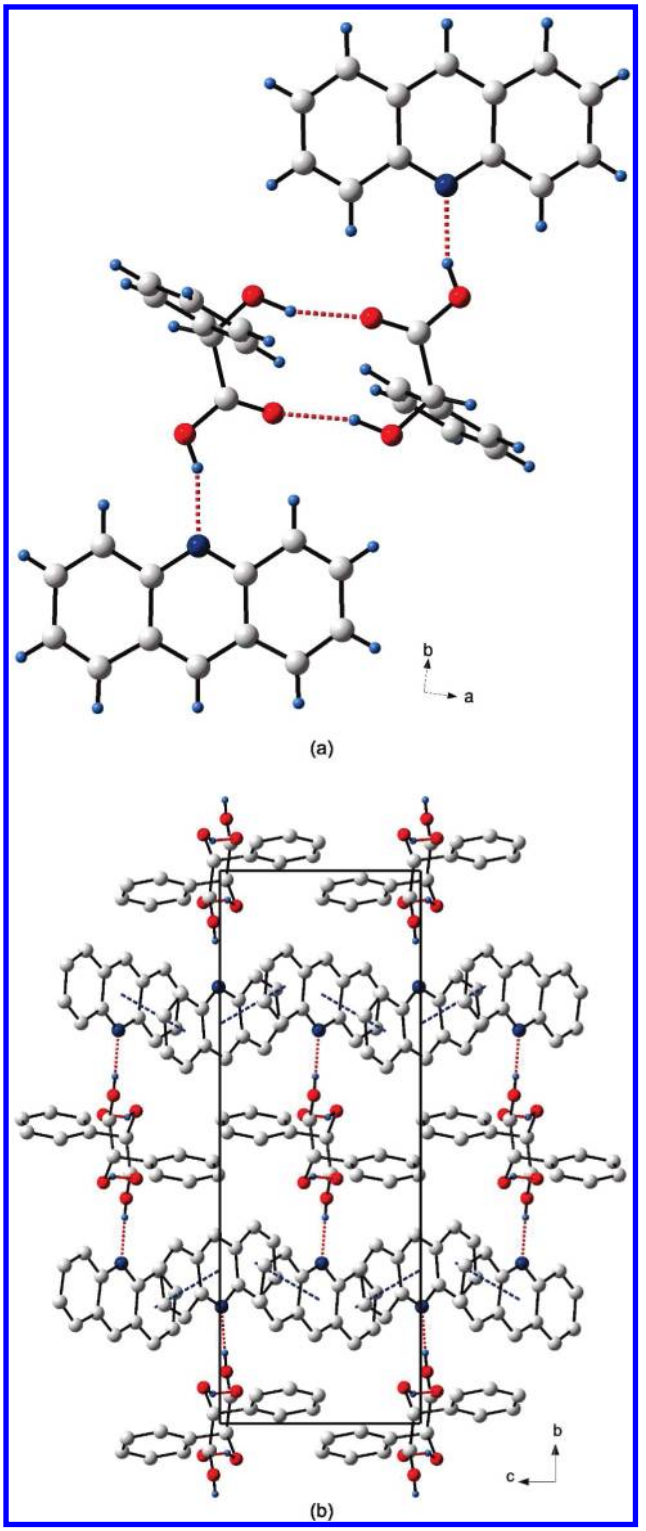

Figure 3. (a) four-membered supermolecule created using O−H···O and O−H···N hydrogen bonds of **2**. (b) Crystal packing of the supermolecules of co-crystal **2** showing the $\pi\cdots\pi$ interactions between the acridine molecules.

of the best available acceptor, the aromatic nitrogen. There are three polymorphs of (*RS*)-mandelic acid[19] reported in the CSD. In all three polymorphs the alcohol proton hydrogen bonds to the acid carbonyl in an $R_2^2(10)$ ring and the carboxylic acid proton

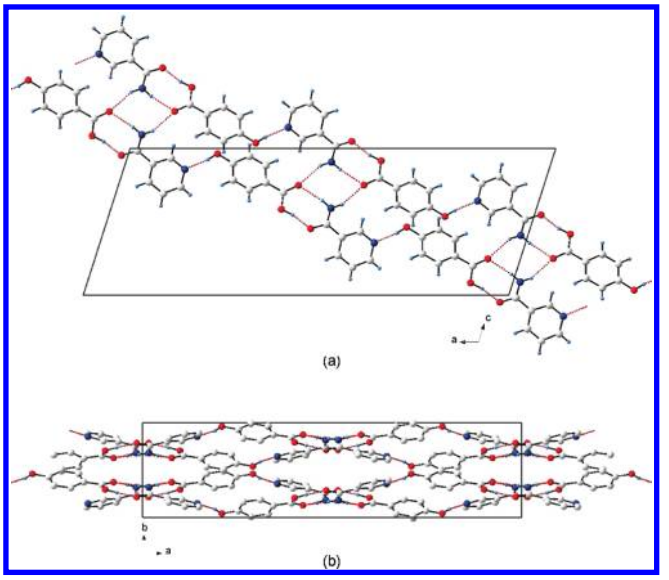

Figure 4. (a) 1D ribbon formed by the O−H···O, N−H···O, and O−H···N hydrogen bonds in co-crystal **3**. (b) Ribbons have a wavelike shape and pack in a parallel arrangement.

hydrogen bonds to an alcohol oxygen in a $C(5)$ chain. Neither the homomeric acid $R_2^2(8)$ dimer nor the homomeric $C(2)$ alcohol chain is observed in any of the three polymorphs. The structure of (*S*)-mandelic acid has two molecules in the asymmetric unit. In both molecules, the alcohol hydrogen bonds to the acid carbonyl and the carboxylic acid proton hydrogen bonds to the alcohol oxygen as seen in the polymorphs of the racemic compound. In the structure of (*S*)-mandelic acid, however, the $R_2^2(10)$ ring is replaced by a $C(5)$ chain. There are only five mandelic acid co-crystals in the CSD reduced set. In two of these, the mandelic acid is racemic and in three of them the mandelic acid is present as a single enantiomer. In all five co-crystal structures the guest compound has at least two good hydrogen acceptors, providing the minimum requirements for one of the Scheme 3 hydrogen-bond patterns. In all five structures, the carboxylic acid proton hydrogen bonds to the guest molecule (in four of the structures the acceptor is an aromatic nitrogen and in one it is a phosphine oxide). No trend, however, is observed in the hydrogen bonding of the alcohol proton. In two structures the alcohol proton also hydrogen bonds to the guest molecule, in two others it hydrogen bonds to the acid carbonyl in a $C(5)$ chain, and in one structure the alcohol hydrogen bonds to an acid OH. In AVIPEA, the alcohol of (*R*)-mandelic acid hydrogen bonds to a phosphine oxide as does the carboxyl proton. In LUNPAL, the alcohol of racemic mandelic acid hydrogen bonds to an anti lone pair of an amide carbonyl which is also involved in a centrosymmetric $R_2^2(10)$ amide dimer. Effectively in this structure the amide dimer has inserted itself into the $R_2^2(10)$ seen previously, forming a centrosymmetric $R_4^4(18)$ ring. The carboxyl proton, in this structure, hydrogen bonds to an aromatic nitrogen. In JILZOU the alcohol proton of (*R*)-mandelic acid hydrogen bonds to the acid carbonyl rather than to the carbonyl of a primary amide in the host. In PIKLEA, the alcohol of (*S*)-mandelic acid also hydrogen bonds to the acid carbonyl in preference to a secondary amide carbonyl. In OFOKEA the alcohol proton of the racemic mandelic acid hydrogen bonds to the acid OH in a 2:1 co-crystal with bipyridine where both of the aromatic nitrogens are hydrogen bonded to carboxylic acid protons.

Table 4. Heteromeric Interactions between Different Functional Groups on Different Molecules in Co-crystals Involving the Six Molecules

	no. of structures	no. and type of homomeric interactions in co-crystals	total no. of heteromeric interactions to various acceptor atoms
m-hydroxybenzoic acid	11	acid dimer: 1	COOH···N: 9
		amide dimer: 1	COOH···O=C−NH2:1
			O=C−N−H···O=C−OH:2
			Ph−OH···N: 7
			Ph−OH···O: 4
TPPO	45	OH···OH: 3	Ph-OH···O=PPh_3: 13
			Ph_3P=O···HO-R: 4
			Ph_3P=O···HN-C=O: 6
			Ph_3P=O···HN-R: 5
			Ph_3P=O···HOOC: 17
			Ph−OH···O=C: 1
mandelic acid	5	amide dimer: 1	COOH···N: 4
		acid dimer: 1	COOH···O=P: 1
			R−OH···O=C−OH: 2
			R−OH···O(H)−C=O: 1
			R−OH···O=C−NH_2: 1
			R−OH···O=P: 1
			R-(H)O···HN-C=O: 1
acridine	16	O−H···O−H: 1	COOH···N: 11
			Ph−OH···N: 2
			R−OH···N: 1
			N−H···N: 2
			R-NH···O=C−OH: 1
p-hydroxybenzoic acid	17	acid dimer: 6	COOH···N: 6
		O−H···O−H: 1	COOH···O=C−NH_2: 3
			COOH···O=C−R: 1
			HO−C=O···HN−C=O: 4
			HO-C=O···HN−R: 2
			Ph−OH···N: 10
			Ph−OH···O=C−OH: 2
			Ph−OH···O=C−R: 3
			Ph−OH···O=C−NH_2: 1
			Ph-(H)O···H−N−C=O: 1
nicotinamide	11	9 amide dimers	COOH···N: 8
		5 amide tetramers	Ph−OH···N: 2
		1 amide chains	O=C−N−H···O=C−OH: 3
			O=C−N−H···O(H)−Ph: 2
			COOH···O=C−NH_2: 1
			R−N-H···O=C−OH: 1
			R−OH···O=C−OH: 1

[a] The number of interactions can exceed the sample size of co-crystal structures used, as most co-crystals have more than one heteromeric interaction.

To date, mandelic acid has produced no 1:2 co-crystals displaying the general pattern shown in Scheme 2. It is interesting to note that even 1:2 solutions of racemic mandelic and acridine result in 1:1 co-crystals.

Acridine, of which there are 16 co-crystals in the reduced set, has predominantly been co-crystallized with acid containing molecules (11*COOH···N) and only with two phenols and one alcohol. Nineteen of the 20 unique acridine molecules in these structures act as hydrogen-bond acceptors. Similarly, as was indicated above for TTPO, the known polymorphs of acridine[18] feature C−H···N or π-stacking interactions, and hence acridine is eminently suitable suitable for co-crystallization experiments with good hydrogen bond donors, as it lacks good donors itself. Acridine itself can also act as a good π-acceptor in the formation of $\pi-\pi$ charge-transfer complexes.[18]

1:1 *p*-Hydroxybenzoic Acid/Nicotinamide Co-crystal 3. The co-crystal between *p*-hydroxybenzoic acid and nicotinamide is a competition experiment between the two donor functionalities on the *p*-hydroxybenzoic acid molecule (phenol and carboxylic acid) and the two acceptor functionalities of the nicotinamide molecule (pyridine and amide carbonyl). An essential component of such a competition experiment is that the same-molecule functional groups be isolated from each other to prevent intramolecular hydrogen bonding from interfering in the competition. This isolation can be easily accomplished by placing groups

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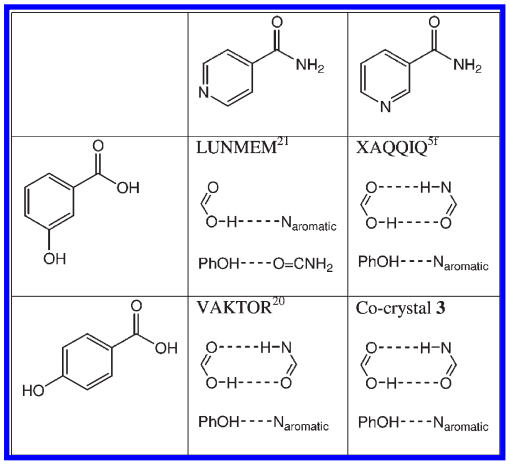
Table 5. Hydrogen-Bonding between Carboxylic Acid and Phenol Donors and Aromatic N and Primary Amide Acceptors in Four Crystal Structures



in a meta or para relationship to each other on an arene backbone. The carboxyl group and the phenol may be combined in *m*-hydroxybenzoic acid or *p*-hydroxybenzoic acid, whereas the pyridine and primary amide groups may be combined in nicotinamide or isonicotinamide. The pair of compounds selected for **3** completes the set of 4 possible pairings of these compounds, the other three previously appearing in the CSD (Table 5).

In the literature, nicotinamide has been predominantly co-crystallized with carboxylic acid containing molecules (9 out of 11 nicotinamide co-crystals found in the CSD)[20] and is a good co-crystal former. This same set of nicotinamide co-crystals features COOH···N eight times, Ph−OH···N twice and the homomeric amide dimer nine times. Hence, both functional groups on *p*-hydroxybenzoic acid can be expected to partner (compete between each other) with the pyridine N of the nicotinamide. In addition, six COOH···N and ten Ph−OH···N hydrogen bonds are observed in the set of 17 *p*-hydroxybenzoic acid co-crystals structures found in the CSD. This further illustrates the ability of both donor types to hydrogen bond to aromatic nitrogens. In co-crystal **3** it is the phenol proton of *p*-hydroxybenzoic acid that hydrogen bonds to the pyridine N atom, whereas the carboxylic acid forms a heterodimer with the amide functional group of nicotinamide. The latter interaction is observed once in the set of nicotinamide:carboxylic acid co-crystals found in the CSD, and is encountered more frequently in co-crystals with isonicotinamide (an isomer of nicotinamide) and carboxylic acids.[16] The fact that the phenol competes with the acid and that the acid competes with homomeric amide dimer formation is a seldom seen case; the first reported one is the isomerically related co-crystal (*p*-hydroxybenzoic acid):(isonicotinamide).[17] This co-crystal features identical heteromeric interactions and a ribbon structure as in **3**, however the ribbon is corrugated and not flat as in **3** due to the different position of the N atom in the pyridine ring. The authors called such a product a minor adduct of a supramolecular reaction (the major adduct would have been one that featured the COOH···N and amide dimer). Co-crystals of *m*-hydroxybenzoic acid with nicotinamide exhibit the same interactions,[5f] whereas isonicotinamide and *m*-hydroxybenzoic acid has the (expected) amide dimer and COOH···N hydrogen bond.[18] Co-crystal **3**, which has two good hydrogen-bonding functional groups each on both molecules, prefers 1:1 co-crystal formation.

When the set of CSD co-crystals involving *m*-hydroxybenzoic acid is combined with the set of CSD co-crystals involving *p*-hydroxybenzoic acid, there are a total of 28 co-crystals. Out of these 28 structures, there are 19 symmetry-independent hydroxybenzoic acid molecules where both the carboxyl and phenolic protons hydrogen bond to the acceptor molecule. This provides strong support for compounds containing both a carboxylic acid and a phenol being good candidates for didonor compounds in ternary co-crystals of the type shown in Scheme 1. There are three examples of hydroxybenzoic acid co-crystals where only the acid donates to an acceptor molecule and seven examples, where only the phenol donates to an acceptor molecule. When only the acid donates to the acceptor molecule, the phenol donates to an acid carbonyl and when only the phenol donates, the acid forms an $R_2^2(8)$ acid dimer. In all three instances where only the acid bonds to the acceptor molecule, it is to an aromatic nitrogen. When only the phenol bonds to the acceptor molecule, it bonds to an aromatic nitrogen (four times), an amide (once), a ketone (once), and an N-oxide (once).

Of the 19 hydroxybenzoic acids where both acid and phenol groups hydrogen bond to the acceptor molecule, nine are bonded to a symmetrical diacceptor compound and seven are bonded to an asymmetrical diacceptor compound. Again, it is the diacceptors with two different acceptor groups that aid in sorting out hydrogen-bond preferences. Although five of the asymmetrical diacceptor molecules have both an aromatic nitrogen and an amide, there was no hint of a selectivity difference between the phenol and the carboxylic acid. In two structures, the acid bonds to the N, whereas the phenol bonded to the amide and in three structures the exact opposite is seen. It is interesting to note that *p*-hydroxybenzoic acid bonds to tetramethylpyrazine only through the carboxyl proton in one structure and only through the phenolic proton in another. In short, on the basis of the available evidence, it appears that given a carboxylic acid, phenol, amide, and aromatic nitrogen there is no preferred pairing of the donors and acceptors. In 2/3 of the examples of the hydroxybenzoic acid co-crystals, both the carboxylic acid and the phenol groups bond to the acceptor molecule and in 1/3 only one of the two donors bonds to the acceptor molecule. The only apparent difference in hydrogen-bonding behavior between *m*-hydroxybenzoic acid and *p*-hydroxybenzoic acid is in the frequency of structures in which the phenol group exclusively hydrogen bonds to the acceptor molecule leaving the carboxylic acid to form an $R_2^2(8)$ acid dimer. Although this occurs in only 1 out of 11 (9%) *m*-hydroxybenzoic acid co-crystals, the phenol dominance is seen in 7 out of 17 (41%) *p*-hydroxybenzoic acid co-crystals. It is useful for comparison purposes that three of the acceptor compounds forming phenol exclusive co-crystals with *p*-hydroxybenzoic acid also form analogous co-crystals with *m*-hydroxybenzoic acid. In one of these, only the carboxylic acid bonds to the acceptor molecule and in the other two, both the acid and the phenol bond to the acceptor molecule.

■ CONCLUSION

In the end, with *m*-hydroxybenzoic acid and *p*-hydroxybenzoic acid, we have two donors on the same molecule that exhibit a number of examples of hydrogen bonding to each of two acceptors, the amide carbonyl and the aromatic nitrogen, but there appears to be little selectivity within this set of four

functional groups even when both donors are appended to the same aromatic ring. Either of these two didonor compounds could be used in designing a ternary co-crystal of the type shown in Scheme 1, but if the two monoacceptor molecules contained an amide and an aromatic nitrogen respectively, it would be nearly impossible to predict which donor would bond to which acceptor. In our third didonor compound, racemic mandelic acid, we have a compound with a carboxylic acid which has a strong affinity for aromatic nitrogens and amide carbonyls and an alcohol, which has unclear loyalties. In the mandelic acid polymorphs and in co-crystal **2**, the alcohol shows a preference for bonding to the mandelic acid carbonyl in a centrosymmetric $R_2^2(10)$ ring, even in crystals grown from a solution with a 2-fold excess of acridine. This preference would have to be broken before this compound would be a viable candidate for ternary co-crystal formation. Using one of the enantiomers of mandelic acid instead of the racemate would break the need for forming the centrosymmetric dimer and possibly increase the affinity of the alcohol for a competing acceptor. The chances of ternary co-crystal formation might also be improved by increasing the distance between the acid and alcohol on the didonor molecule.

In conclusion, we have demonstrated that through (a) synthesizing didonor/monoacceptor co-crystals and didonor/diacceptor co-crystals of the types shown in Schemes 1 and 2 from solutions of varying mole ratios and (b) using the Cambridge Structural Database for investigating the hydrogen-bond histories of the compounds of interest, we can gain valuable insight into the viability of specific didonor compounds for potential ternary co-crystal synthesis.

■ ASSOCIATED CONTENT

Supporting Information. X-ray crystallographic information files CIF (**1**−**3**); H NMR and IR data for **1** and **2** (PDF); and cif, pdf files, and co-crystal breakdown of the CSD searches. This material is available free of charge via the Internet at http://pubs.acs.org.

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