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Synthon Modularity in Cocrystals of 4-Bromobenzamide with *n*-Alkanedicarboxylic Acids: Type I and Type II Halogen···Halogen Interactions

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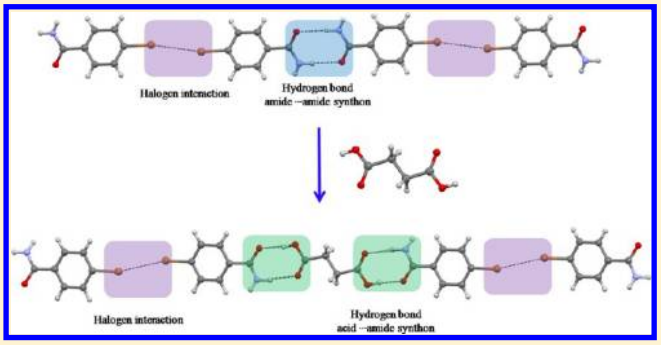
Supporting Information

ABSTRACT: A Cambridge Structural Database (CSD) analysis on halogen···halogen contacts (X···X) in organic crystals has been carried out to review the classification criteria for type I, type II, and quasi type I/II halogen interactions. Trends observed in previous CSD analyses of the phenomenon are reinforced in the present study. The manner in which these interactions are manifested in cocrystals of 4-bromobenzamide and dicarboxylic acid is examined. The design strategy for these cocrystals uses synthon theory and follows from an understanding of the crystal structures of γ-hydroquinone and a previously studied set of 4-hydroxybenzamide dicarboxylic acid cocrystals, making use of Br/OH isostructurality. All cocrystals are obtained by clean insertion of dicarboxylic acids between 4-bromobenzamide molecules. The strategy is deliberate and the prediction of synthons done well in advance, as evidenced from the robustness of the acid−amide heterosynthons in all nine crystal structures, with no aberrant structures in the crystallization experiments. Formation of the acid−amide synthon in these cocrystals is identified with IR spectroscopy. The packing in these cocrystals can be distinguished in terms of whether the Br···Br interactions are type I or II. Eight sets of dimorphs were retrieved from the CSD, wherein the basis of the polymorphism is that one crystal has a type I Br···Br interaction, while the other has a type II interaction.



INTRODUCTION

When the supramolecular synthons[1] and the packing modes in a crystal structure are repeated in compounds that share some molecular functionalities, a certain degree of what might be termed synthon modularity is obtained. Such modularity is advantageous because it means that a particular crystal packing with a particular synthon or synthons that is found in one crystal structure is likely to be seen in another system without prejudice from other molecular functionalities that might or might not be present.[2] Very recently, we have reported on cocrystals of 4-hydroxybenzamide with aliphatic dicarboxylic acids based on O−H···O−H synthon similarity (phenol···phenol) to the crystal structures of γ-quinol, 4,4′-biphenol, and 4-hydroxybenzoic acid.[2] Our strategy also used the robustness of the acid−amide heterosynthon[3] to form a 2:1 amide−acid aggregate.[2] Effectively, acid−amide and phenol−phenol synthons are insulated in the cocrystals, and it is pertinent to note that the cooperative O−H···O−H chain synthon that is observed in the single component 4-hydroxybenzamide remained intact after insulating the acid−amide synthon with long chain diacids. The reminiscence of these intermolecular interactions present in single components in the cocrystals enables one to envisage further design strategies.[4] To rationalize this theme, the OH functional group can be replaced with a functional group analog, namely the heavier halogen, Br. Isostructurality of the OH/Br type is well-known, as manifested in the similar topologies of the crystal structures of γ-quinol and 1,4-dibromobenzene; other single component systems, wherein this supramolecular similarity of Br and OH is seen, have been described.[5] However, such Br/OH isostructurality has not been systematically explored for cocrystals.

Crystal engineering is the design of new crystals with desired properties generally from prior understanding of known crystal structures.[6] The role of halogen bonding in crystal engineering has drawn substantial attention from researchers.[7] Typically, difficulties are encountered during crystallization in the selection of a predefined molecular packing because of interference from strong competitor interactions on the one hand and the tendency toward a close-packed structure on the other.[8] In this context, the moderately strong halogen interactions can be used to induce crystal packing in a predefined manner.[9] The use of halogen interactions, which lie energetically and directionally between the strong classical hydrogen bonds[10] and the weak and less directional C−H···O/N hydrogen bonds, could provide a proactive route in crystal engineering.[11] Accordingly, we set about to prepare and characterize cocrystals of 4-bromobenzamide and the same aliphatic diacids used in our earlier study.[2]

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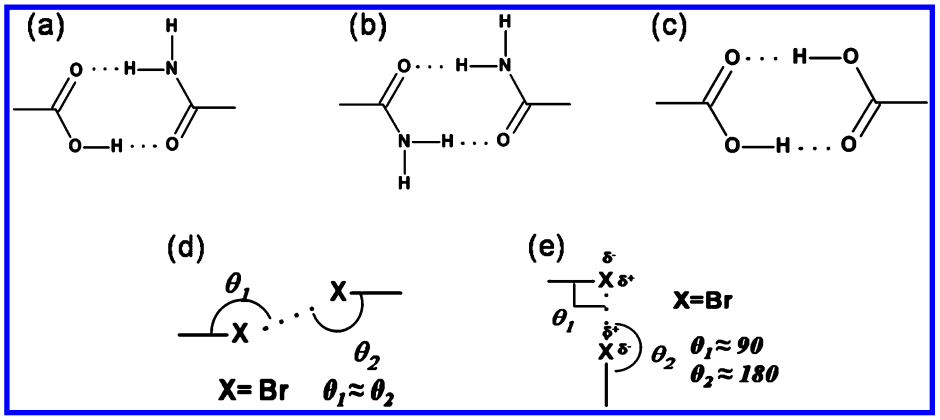
Scheme 1. Hydrogen Bond and Halogen Interactions in Design Strategy for Cocrystals of 4-Bromobenzamide with Dicarboxylic Acids: (a) Acid−amide, (b) Amide−amide, (c) Acid−acid, (d) Type I, and (e) Type II Halogen Interactions



EXPERIMENTAL SECTION

CSD Analysis Criteria. CSD structural data analysis was carried out with version 5.34 (November 2012, including two updates).[12] The analysis was confined to purely organic compounds. No restrictions were kept in terms of the R-factor range, disorder, polymeric, ions, or powder structure. The geometrical constraints were given using ConQuest 1.15. Unique intermolecular interactions were considered for symmetrical and unsymmetrical X···X interactions, up to the sum of the van der Waals radii (Cl···Cl, 3.50; Br···Br, 3.70; I···I, 3.96; Cl···F, 3.22; Br···F, 3.32; I···F, 3.45; Br···Cl, 3.60; I···Cl, 3.72; I···Br, 3.83 Å). The retrieved data was used for further analysis and classification. For symmetrical $X_1 \cdots X_2$ interactions ($X_1 = X_2$), $|\theta_1 - \theta_2|$ was calculated and used to plot histograms of the differences in angle $|\theta_1 - \theta_2|$ at intervals of 5° versus the number of contacts. The classification thus arrived for type I, type II, and quasi type I/type II was used for plotting distance (from vdW − 0.2 to vdW + 0.10 Å) at intervals of 0.05 Å versus percentage of number of type I and type II contacts.

Single Crystal X-ray Crystallography. Single crystal X-ray data for all cocrystals were collected on a Rigaku Mercury 375/M CCD (XtaLAB mini) diffractometer using graphite monochromated Mo Kα radiation at 150 K. The data were processed with Rigaku CrystalClear.[13] Refinement of coordinates and anisotropic thermal parameters of nonhydrogen atoms were performed with the full-matrix least-squares method.[14] The different treatment of H atoms in any structure depends on the data quality. In most of the cases, the hydrogen atoms in NH_2 and OH groups were located from different Fourier maps. In certain cases, the CH hydrogen atoms were calculated using the riding model. PLATON[15] was used to prepare material for publication, and Mercury version 3.1 was utilized for molecular representations and packing diagrams.

Powder X-ray diffraction (PXRD). X-ray powder diffraction (PXRD) data, for 4-bromobenzamide, oxalic acid, and 4-bromobenzamide-oxalic acid crystals, were collected on a Philips X'pert Pro X-ray powder diffractometer equipped with an X'cellerator detector. The scan range was 2θ = 5 to 40°. Since the 4-bromobenzamide-oxalic acid crystal quality was not good enough for a single crystal structural study, PXRD patterns were recorded to confirm cocrystal formation (Figure 1S of the Supporting Information).

IR Spectroscopy. IR data for all cocrystals were collected on a Perkin-Elmer Spectrum-1000 Fourier transform-infrared (FT-IR) spectrometer in the range from 300 to 4000 cm^{-1}. All spectra were recorded on KBr pellets.

Crystallization. *4-Bromobenzamide:Malonic Acid 2:1 Cocrystal (**1**).* 4-Bromobenzamide and malonic acid were taken in a 2:1 molar ratio and ground after adding 2−3 drops of EtOH (solvent drop grinding).[16] The ground sample was dissolved in a minimum amount of MeOH. Good quality crystals, suitable for diffraction, were obtained after two days (mp: 153−155 °C).

*4-Bromobenzamide:Fumaric Acid 2:1 Cocrystal (Form I) (**2**).* 4-Bromobenzamide and fumaric acid were taken in a 2:1 molar ratio and ground using mortar and pestle after adding 2−3 drops of EtOH. The ground sample was dissolved in a minimum amount of MeOH. Good quality crystals, suitable for diffraction, were obtained after four days (mp: 238−240 °C).

*4-Bromobenzamide:Succinic Acid 2:1 Cocrystal (Form I) (**3**).* 4-Bromobenzamide and succinic acid were taken in a 2:1 molar ratio and ground using mortar and pestle after adding 2−3 drops of EtOH. The ground sample was dissolved in 1:1 MeOH−1,4-dioxane. Good quality crystals, suitable for diffraction, were obtained after one week (mp: 168−170 °C).

*4-Bromobenzamide:Adipic Acid 2:1 Cocrystal (**4**).* 4-Bromobenzamide and adipic acid were taken in a 2:1 molar ratio and ground after adding 2−3 drops of EtOH. The ground sample was dissolved in a minimum amount of CH_3NO_2. Good quality crystals, suitable for diffraction, were obtained after six days (mp: 157−159 °C).

*4-Bromobenzamide:Pimelic Acid 2:1 Cocrystal (**5**).* 4-Bromobenzamide and pimelic acid were taken in a 2:1 molar ratio and ground after adding 2−3 drops of EtOH. The ground sample was dissolved in a minimum amount of MeOH. Good quality crystals, suitable for diffraction, were obtained after five days (mp: 149−152 °C).

*4-Bromobenzamide:Suberic Acid 2:1 Cocrystal (**6**).* 4-Bromobenzamide and suberic acid were taken in a 2:1 molar ratio and ground after adding 2−3 drops of EtOH. The ground sample was dissolved in a minimum amount of MeOH. Good quality crystals, suitable for diffraction, were obtained after four days (mp: 161−163 °C).

*4-Bromobenzamide:Sebacic Acid 2:1 Cocrystal (**7**).* 4-Bromobenzamide and sebacic acid were taken in a 2:1 molar ratio and ground after adding 2−3 drops of EtOH. The ground sample was dissolved in a minimum amount of *i*-PrOH. Good quality crystals, suitable for diffraction, were obtained after one week (mp: 142−144 °C).

*4-Bromobenzamide:Fumaric Acid 4:1 Cocrystal (Form II) (**8**).* 4-Bromobenzamide and fumaric acid were taken in a 2:1 molar ratio and ground in a mortar with a pestle after adding 2−3 drops of EtOH. The ground sample was dissolved in a minimum amount of THF. Good quality crystals, suitable for diffraction, were obtained after five days.

*4-Bromobenzamide:Succinic Acid 4:1 Cocrystal (Form II) (**9**).* 4-Bromobenzamide and succinic acid were taken in a 2:1 molar ratio and ground after adding 2−3 drops of EtOH. The ground sample was dissolved in a minimum amount of THF. Good quality crystals, suitable for diffraction, were obtained after four days.

4-Bromobenzamide:Oxalic Acid Cocrystal. 4-bromobenzamide−oxalic acid cocrystal was obtained from MeOH, but the crystal quality was not good for single crystal work. The phase formation was confirmed from the PXRD pattern and a melting point (226 °C) was obtained from the hot stage microscope (HSM) (Figure 2S of the Supporting Information).

RESULTS AND DISCUSSION

Halogen···Halogen Interactions. Noncovalent halogen···halogen interactions have been the subject of much recent

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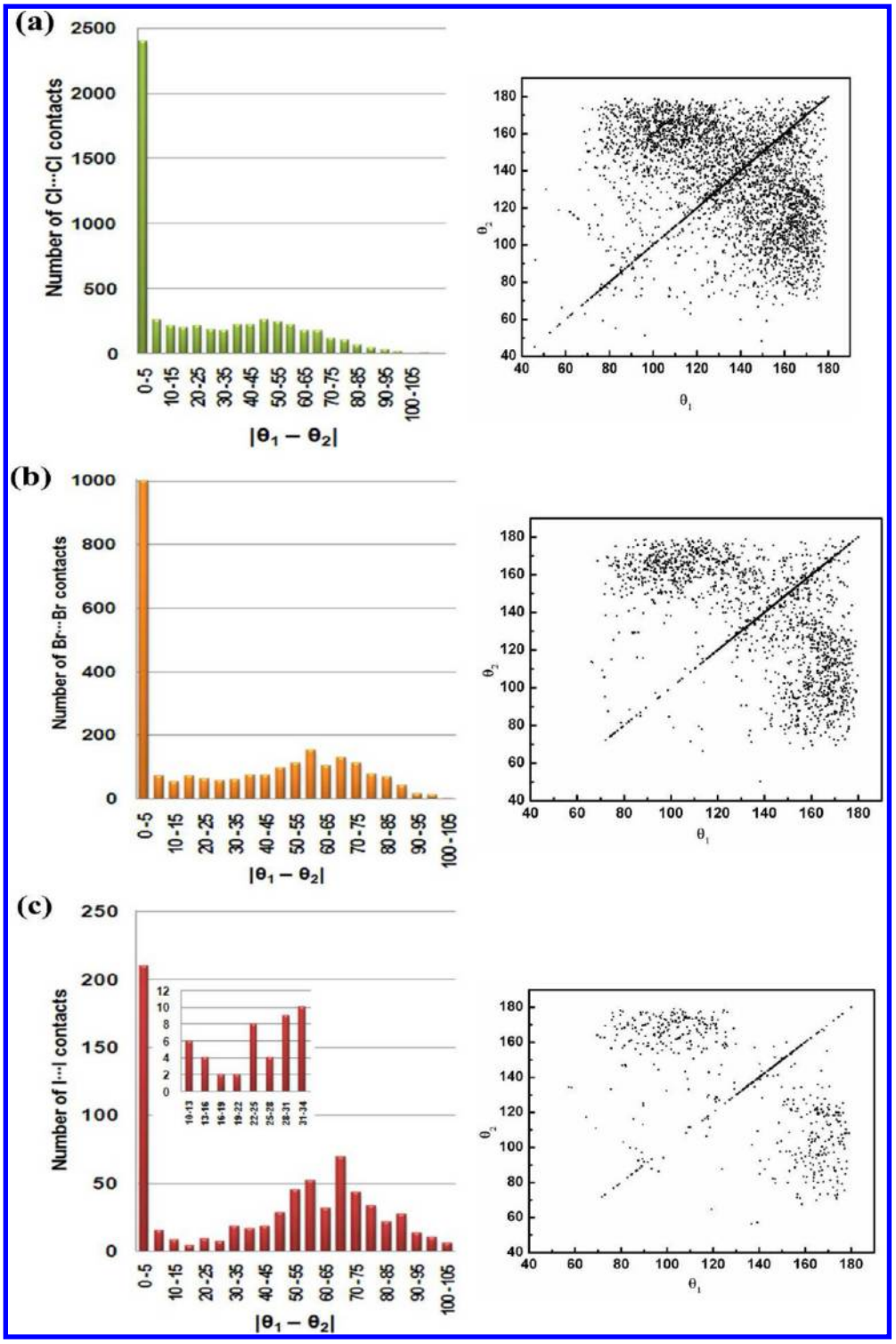

Figure 1. Histograms of the difference in angle $|\theta_1 - \theta_2|$ at intervals of 5° versus number of contacts for (a) Cl···Cl, (b) Br···Br, and (c) I···I contacts. The corresponding scattergrams are plotted on the right-hand side.

interest in crystal engineering.[7] Many years ago, the directional preferences in these interactions/short contacts were noticed and classified as type I and type II by Sakurai, Sundaralingam, and Jeffrey.[17] An article based on a statistical analysis from the CSD of short X···X interactions in all halogenated compounds was published by Parthasarathy and Desiraju in 1989.[18] The attractive nature of halogen···halogen short approaches was emphasized in that paper. The reason for this conclusion is that the number of X···X contacts are much higher than what would have been expected on purely statistical grounds. Later on, in 1994, a more detailed and systematic CSD analysis was carried out, based on 794 structures of halogenated organic compounds, and a simplified classification was put forward.[19] This work concluded that in type I interactions, the close contact may be attributed to close packing, while the type II contacts arise from electrostatic attractions between polarized

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Table 1. Summary of Symmetrical Halogen···Halogen (X_1···X_2) Interactions ($X_1 = X_2$) Obtained from CSD Search

interactions	compounds	total contacts	type I	quasi type I/type II	type II
Cl···Cl	3731	5586	2883 (52%)	604 (11%)	2099 (37%)
Br···Br	1871	2452	1125 (46%)	191 (8%)	1136 (46%)
I···I	530	683	233 (34%)	20 (3%)	430 (63%)

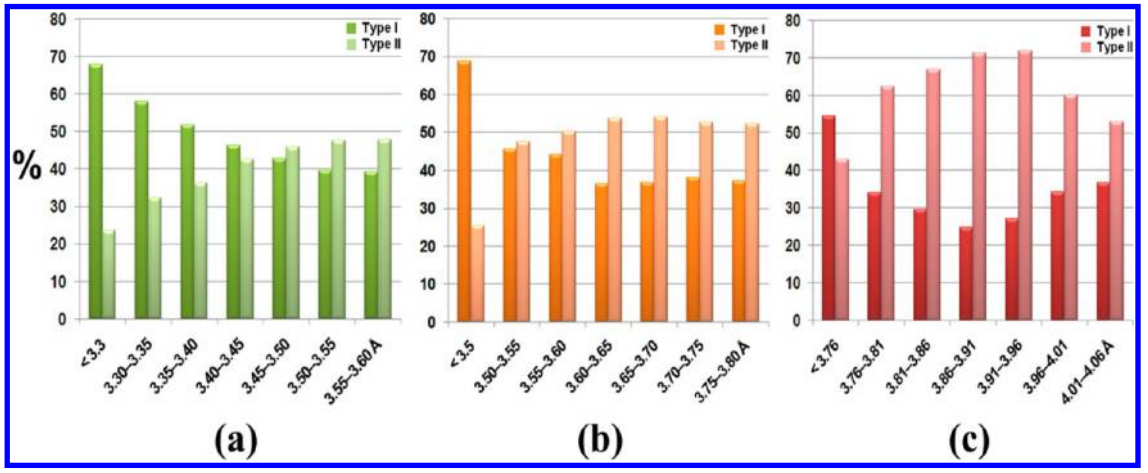

Figure 2. Histograms of X_1···X_2 interaction ($X_1 = X_2$) distance (from vdW − 0.2 to vdW + 0.10 Å) at intervals of 0.05 Å vs percentage of number of type I and II contacts for (a) Cl···Cl, (b) Br···Br, and (c) I···I.

atoms ($X^{\delta+}$···$X^{\delta-}$). From the scattergrams in that study, a demarcation could be observed between type I and type II. Also, as the polarizability increases (Cl < Br < I), type II contacts became relatively more significant when compared to type I. Now, with the latest 5.34 version of the CSD,[12] a total of 6974 organic crystal structures with the X···X interactions are available. In order to draw surer chemical conclusions, we revisited the analyses given in our 1989 and 1994 papers. We plotted histograms of the differences in angle $|\theta_1 - \theta_2|$ at intervals of 5° versus the number of contacts (Figure 1). The corresponding scattergrams are plotted on the right-hand side. In both histograms and scattergrams, a clear demarcation is observed between types I and II. The $|\theta_1 - \theta_2| = 0-5°$ region has the highest frequency per interval in all the histograms, if the interval is taken as 5°. The rest of the histogram is an unsymmetrical curve for Cl···Cl; this becomes more symmetrical for Br···Br with a clear dip at around $|\theta_1-\theta_2| = 15-30°$ between type I and type II regions. This dip becomes even more prominent for I···I, making a symmetrical curve in the type II region. Therefore the I···I histogram is an ideal model for the classification. The shallow region in the I···I histogram yields further details under closer examination. The number of contacts decreases gradually to a minimum at ∼16−22°. Then there is a small increase in the contacts observed at ∼22−25°, followed again by a descent. This small discernible maximum is observed for all three halogens when $|\theta_1 - \theta_2| \approx 20-25°$. Taking all this together, we suggest that contacts with $0° \le |\theta_1 - \theta_2| \le 15°$ are classified as type I, those with $30° \le |\theta_1 - \theta_2|$ are classified as type II, while those with $15° \le |\theta_1 - \theta_2| \le 30°$ are classified as quasi type I/type II interactions. The highest population for pure type II is observed in the region of $|\theta_1 - \theta_2| = 45-50°$ for Cl···Cl, 55−60° for Br···Br, and 65−70° for I···I interactions, indicating that as the polarizability increases, the angular attributes of the type II interaction become more sharply demarcated and this follows from the more electrostatic nature of these contacts, that are less influenced by close packing factors. Many short type I Cl···Cl contacts are of the van der Waals type due to the smaller polarizability of Cl and may be considered as essentially space filling in nature, whereas I···I contacts are of the "chemical" type due to induced polarization of the I atom or inherent asymmetric distribution of the electron density around this heavy halogen; they can be considered as being more electrostatic in nature. Rigorously speaking, no X···X interaction in which $\theta_1 \neq \theta_2$ can be taken as fully geometrical or fully chemical in nature. But, as one moves from Cl···Cl to I···I, the demarcation between types I and II becomes quite exceptional, and the type II contacts become predominantly "chemical" in nature.

The angular ranges for classification being thus confirmed, and in order to get details of the numbers of structures in each category, we carried out a CSD analysis of the X···X interactions in each category. The results are given in Table 1. For symmetrical X_1···X_2 interactions ($X_1 = X_2$), type I occurs more often for Cl, whereas the number of contacts exhibiting types I and II is nearly the same for Br. But for I, where more polar flattening is possible, the number of type II interactions (63%) is higher than type I. In type I, the short interatomic distances are a consequence of close packing rather than any directional interactions. Therefore, such contacts are repulsive at shorter separations. As the polarizability increases, the tendency to form type I interactions diminishes. The quasi type I/type II region shows a decrease in the number of contacts from 11% in Cl···Cl to 3% in I···I.

The percentage of type I and type II contacts were compared as a function of interaction distance (Figure 2). In all cases, type I predominates at very short contact distances (vdW − 0.2 Å). For Cl···Cl, type I is more numerous up to the van der Waals distance −0.05 Å. For Br···Br and I···I, at a van der Waals distance of −0.15 Å, the percentage of type II exceeds type I. Type II interactions are electrostatics-based and can operate through preferred trajectories at longer distances, typically even greater than the van der Waals separation. To summarize, it is not so necessary for type II interactions to have very short distances and this accounts for the distance distributions

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discussed above. In other words, type I interactions are important at very short distances for all three halogens and the distance falloff shows an abruptly diminishing behavior characteristic of a van der Waals interaction. Put differently, very long type I interactions do not seem to contribute significantly in a chemical sense. Still, there is more than a hint that geometrical factors operate. There is a definite increase in the type I I···I contacts at long separations and this could be indicative of the fact that the I atom is much larger than Br or Cl. Accordingly, size factors could lead to the adoption of a type I geometry for I···I. This increase in type I at long separations is actually even (just) discernible for Br. In the end, one arrives at the conclusion that both chemical (polarization, electrostatic) and geometrical (size, space filling) factors need to be taken into account when assessing an X···X interaction. The analogy between a halogen bond and a hydrogen bond should not be taken too far.

For the unsymmetrical $X_1\cdots X_2$ contacts ($X_1 \neq X_2$), there are obviously no "pure" type I interactions (Table 2). Heavier

Table 2. Summary of Unsymmetrical Halogen···Halogen ($X_1\cdots X_2$) Interactions ($X_1 \neq X_2$) (CSD Search)[a]

			type II			
interactions	compounds	total contacts	$N_{\theta1>\theta2}$	$N_{\theta2>\theta1}$	$N_{\theta1>\theta2}/N_{\theta2>\theta1}$	$\Delta\chi$
Cl···F	364	514	330	184	1.793	0.82
Br···F	132	190	133	57	2.333	1.02
I···F	69	84	61	23	2.652	1.32
Br···Cl	210	256	153	103	1.485	0.2
I···Cl	39	47	31	16	1.938	0.5
I···Br	28	43	30	13	2.308	0.3

[a] θ_1 = C−$X_{heavy}\cdots X_{light}$; θ_2 = C−$X_{light}\cdots X_{heavy}$.

halogens can act as electron donors as well as electron acceptors, due to polarization. The interactions are categorized into two groups based on the values of θ_1 and θ_2 (where θ_1 = C−$X_{heavy}\cdots X_{light}$, and θ_2 = C−$X_{light}\cdots X_{heavy}$). Since the heavier halogens undergo more polar flattening, $\theta_1 > \theta_2$ is favored over $\theta_2 > \theta_1$, due to electrostatic reasons. A plot of $\Delta\chi$ versus $N_{\theta1>\theta2}/N_{\theta2>\theta1}$ is given in Figure 3. As the difference in electronegativity increases, there is a continuous increase in the ratio of $N_{\theta1>\theta2}/N_{\theta2>\theta1}$.

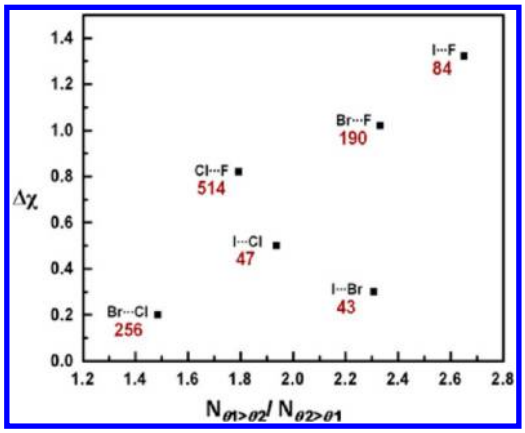


Figure 3. Plot of difference in electronegativity ($\Delta\chi$) vs $N_{\theta1>\theta2}/N_{\theta2>\theta1}$ in unsymmetrical $X_1\cdots X_2$ contacts ($X_1 \neq X_2$). The total number of contacts is indicated under the symbol.

Cocrystal Formation. Cocrystals[20] are formed by incorporation of diacids between amide−amide homodimers of 4-bromobenzamide because of the preferential formation of acid−amide heterosynthons. The design strategy is given in Scheme 2.

In this paper, we have studied cocrystals of 4-bromobenzamide with aliphatic diacids. Since acid−amide synthon formation is preferred over acid−acid or amide−amide, the formation of the heterosynthon is expected. A Br···Br nonbonding interaction also is anticipated, since no other interactions are possible.

The final point of interest is whether the Br···Br contact is type I or II in the cocrystal. This becomes relevant because 4-bromobenzamide exists in two polymorphic modifications, with the Br···Br contact being type I and type II in the two polymorphs, respectively.[21] Since the reported structures (of 4-bromobenzamide) are not well-resolved and hydrogen atom positions have not been determined, we carried out these analyses again to better the R factors. Form I is obtained by crystallization from a 1:1 mixture of MeOH/EtOAc. Form II is obtained by crystallization from pure *i*-PrOH or from a 1:1 mixture of MeOH/MeCN or 1:1 MeOH/acetone. In THF, both forms were obtained concomitantly. Form I ($P\bar{1}$) is characterized by the amide−amide homosynthon and a type I Br···Br interaction (Br···Br = 3.501 Å and $\theta_1 = \theta_2 = 166.5°$) (Figure 4). Form II crystallizes in the space group $P2_1/a$ and also has the amide−amide homosynthon, but the Br···Br contact is now type II (Br···Br = 3.578 Å, $\theta_1 = 90.9°$, and $\theta_2 = 171.1°$).

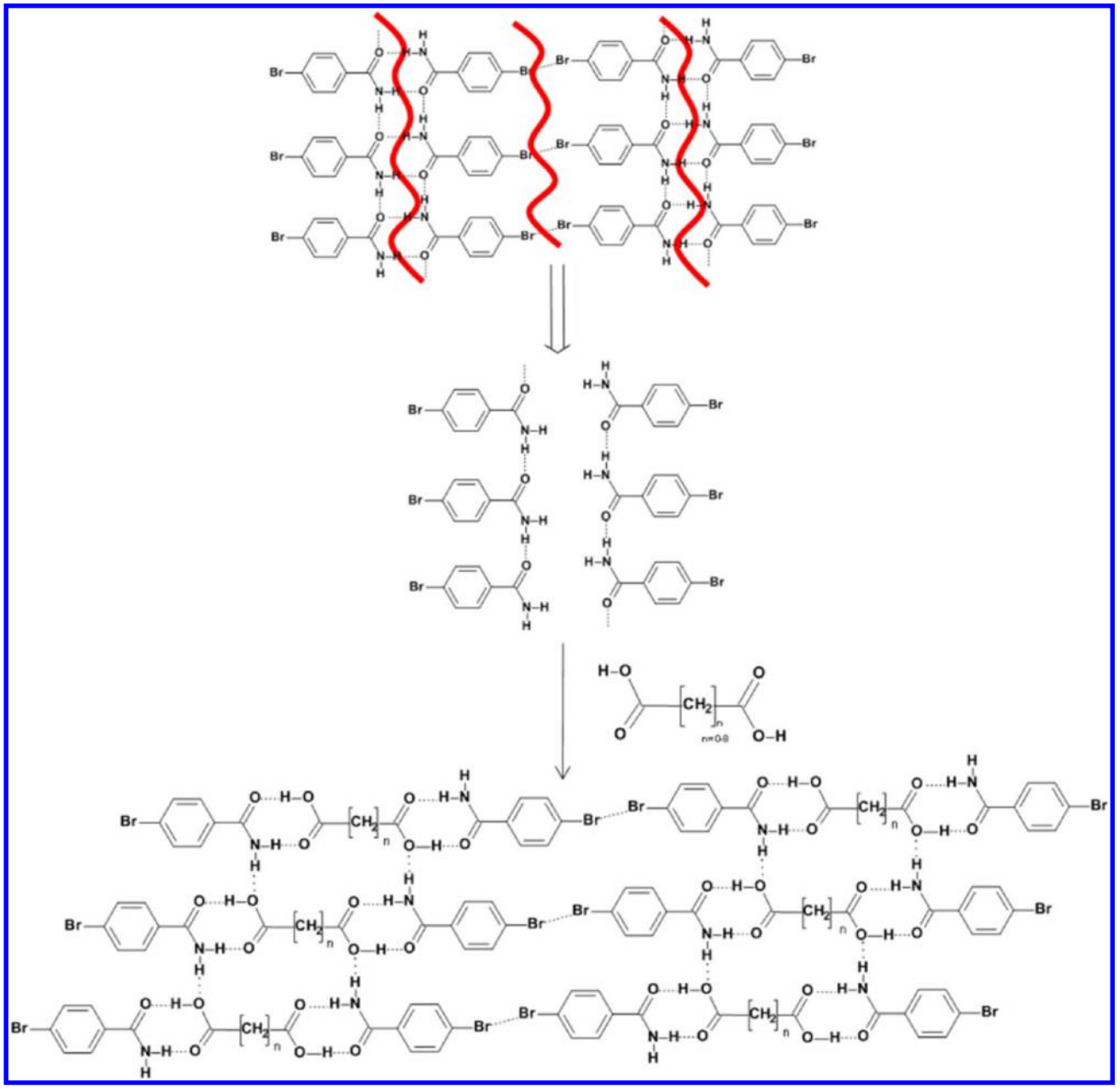
*4-Bromobenzamide:Malonic Acid 2:1 Cocrystal (**1**).* Molecules are associated with the acid−amide synthon and Br···Br interactions (Br···Br = 3.605 Å, $\theta_1 = 141.4°$, and $\theta_2 = 171.8°$) and crystallize in the space group $P2_1/c$ with two molecules of 4-bromobenzamide and one molecule of malonic acid in the asymmetric unit ($Z'' = 3$). The Br···Br contact is quasi type I (as defined earlier in this paper) (Figure 5). For all cocrystals, crystallographic data and structure refinement parameters are shown in Table 3.

*4-Bromobenzamide:Fumaric Acid 2:1 Cocrystal (Form I) (**2**).* The structure takes the $P2_1/c$ space group with two molecules of 4-bromobenzamide and one molecule of fumaric acid in the asymmetric unit ($Z'' = 3$). Molecules are connected with the acid−amide heterosynthon and a Br···Br type I interaction (Br···Br = 3.423 Å, $\theta_1 = 153.5°$, and $\theta_2 = 152.5°$). Consecutive layers related by the 2_1 axis are connected by N−H···O and C−H···O hydrogen bonds (Figure 6).

*4-Bromobenzamide:Succinic Acid 2:1 Cocrystal (Form I) (**3**).* The space group is $P\bar{1}$ with one molecule of 4-bromobenzamide and a half molecule of succinic acid ($Z'' = 1.5$). The fact that succinic acid is an analog to fumaric acid is reflected in the intermolecular interactions. The acid−amide, Br···Br interactions (Br···Br = 3.420 Å, $\theta_1 = \theta_2 = 162.1°$) and secondary N−H···O and C−H···O hydrogen bonds are essentially the same as in the 4-bromobenzamide:fumaric acid 2:1 cocrystal form I. (Figure 7).

*4-Bromobenzamide:Adipic Acid 2:1 Cocrystal (**4**).* Crystals were obtained in the $P\bar{1}$ space group with one molecule of 4-bromobenzamide and a half molecule of adipic acid ($Z'' = 1.5$). Again the acid−amide synthon and Br···Br contacts (Br···Br = 3.429 Å, $\theta_1 = \theta_2 = 148.8°$) (Figure 8) are prominent interactions. Here, two consecutive layers are connected by N−H···O hydrogen bonds. The molecular packing is similar to 4-bromobenzamide:succinic acid 2:1 cocrystal form I.

Scheme 2. Design of Cocrystals of 4-Bromobenzamide and Dicarboxylic Acids with Hydrogen Bonds and Halogen Interactions



*4-Bromobenzamide:Pimelic acid 2:1 Cocrystal (**5**).* The space group is $C2/c$ with one molecule of 4-bromobenzamide and a half molecule of pimelic acid ($Z'' = 1.5$). The infinite Br···Br···Br chain (Br···Br = 3.793 Å, $\theta_1 = 126.8°$, and $\theta_2 = 149.8°$) in this structure is similar to the O−H···O−H···O−H··· cooperative infinite chain that is present in the 4-hydroxybenzamide-dicarboxylic acid cocrystals. The structure has a ladderlike appearance (Figure 9).

*4-Bromobenzamide:Suberic Acid 2:1 Cocrystal (**6**).* Molecules are associated with the acid−amide synthon and type I Br···Br interactions (Br···Br = 3.465 Å, $\theta_1 = \theta_2 = 154.3°$) and adopt space group $P\bar{1}$ with one molecule of 4-bromobenzamide and a half molecule of suberic acid in the asymmetric unit ($Z'' = 1.5$). The packing is similar to that in cocrystals of 4-bromobenzamide with succinic and adipic acids (Figure 10).

*4-Bromobenzamide:Sebacic Acid 2:1 Cocrystal (**7**).* The structure takes the $P\bar{1}$ space group and the crystal packing and synthons are similar to the above-discussed even-acid cocrystals with type I Br···Br interactions (Br···Br = 3.653 Å, $\theta_1 = \theta_2 = 152.1°$) (Figure 11). The asymmetric unit consists of one molecule of 4-bromobenzamide and a half molecule of sebacic acid ($Z'' = 1.5$)

*4-Bromobenzamide:Fumaric Acid 4:1 Cocrystal (Form II) (**8**).* The structure takes the $P2_1/c$ space group with four molecules of 4-bromobenzamide and one molecule of fumaric acid ($Z'' = 5$) in the asymmetric unit. This amide-rich stoichiometry manifests itself in the fact that amide−amide dimers are present along with the expected (designed) acid−amide synthons, which appear as a three-molecule aggregate. Both the 2:1 amide−acid aggregate and the amide−amide dimer form three type II Br···Br contacts ($Br_1···Br_2$ = 3.494 Å, $\theta_1 = 79.5°$, and $\theta_2 = 162.1°$; $Br_1···Br_4$ = 3.741 Å, $\theta_1 = 79.8°$, and $\theta_2 = 160.6°$; and $Br_3···Br_4$ = 3.710 Å, $\theta_1 = 86.5°$, and $\theta_2 = 153.7°$) that are similar to those seen in the second polymorph

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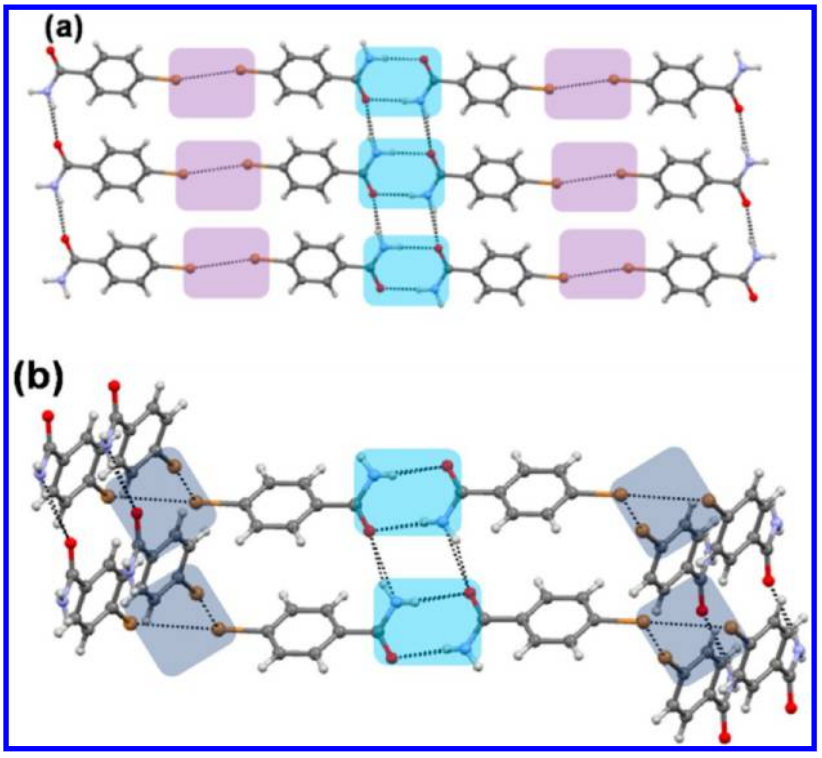

Figure 4. 4-Bromobenzamide dimorphs: Both forms are stabilized by the amide−amide heterosynthon, and the only difference is in the type of Br···Br interaction. They are color coded blue (amide−amide synthon), pink (type I halogen interaction), and gray (type II halogen interaction).

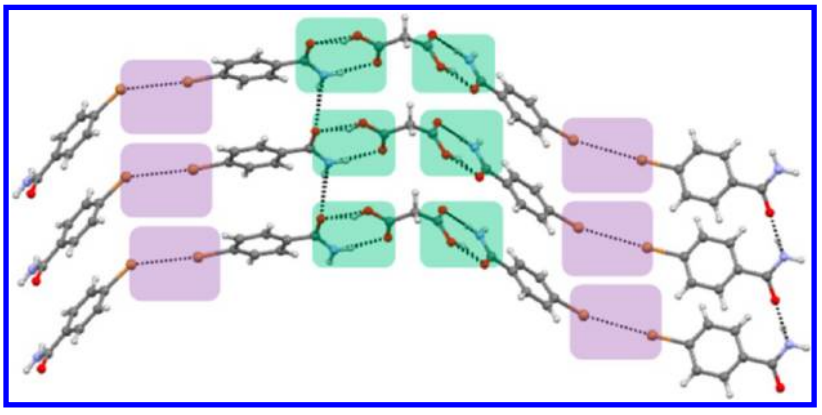

Figure 5. 4-Bromobenzamide:malonic acid 2:1 cocrystal (**1**), crystal packing stabilized by acid−amide heterosynthon and quasi type I halogen interaction, are highlighted with green and pink colors, respectively. They are color-coded green (acid−amide synthon) and pink (type I/quasi type I halogen interaction).

of 4-bromobenzamide. The aggregate and dimer arranged perpendicular to each other is connected by type II Br···Br contacts (Figure 12).

*4-Bromobenzamide:Succinic Acid 4:1 Cocrystal (Form II) (**9**).* Isostructurality in cocrystals has been studied previously.[22] The 4:1 cocrystal of succinic acid is isostructural with that of fumaric acid (**8**), owing to its analogous molecular characteristics.[2,22h,i] The intermolecular interactions and molecular packing in **9** and **8** are also the same ($Br_1\cdots Br_2$ = 3.509 Å, θ_1 = 80.4°, and θ_2 = 162.9°; $Br_3\cdots Br_4$ = 3.671 Å, θ_1 = 86.3°, and θ_2 = 156.7°; and $Br_1\cdots Br_4$ = 3.698 Å, θ_1 = 80.2°, and θ_2 = 161.4°) (Figure 13).

Halogen···Halogen Type I-/Type II-Based Polymorphism. The complex nature of the crystallization event makes the phenomenon of polymorphism still inscrutable. The presence of synthons in solution, the nucleation event, and subsequent growth of a phase need be explored. 4-Bromobenzamide exists in two polymorphic modifications. A very interesting aspect of the polymorphism in this compound is that it is characterized by a difference in the halogen-bonding interactions. We carried out a CSD search for organic compounds that show polymorphism based on whether type I or type II Br···Br interactions are formed. Out of 1871 structures, which have short Br···Br contacts, only eight compounds are found that show this type of polymorphism; in other words, where the Br···Br contacts are types I and II, respectively, in the two polymorphs. A more detailed analysis of these eight structures shows that only in one case are the polymorphs obtained exclusively from different solvents.[29] The polymorphism is not solvent induced in the other structures and both the forms are formed concomitantly under similar conditions in four of them.[21,23,25,26] In the remaining three

Table 3. Crystallographic Data and Structure Refinement Parameters for the Compounds in This Study[a]

	1	2	3	4	5	6	7	8	9	10	11
	4BRBZ:MA	4BRBZ:FA form I	4BRBZ:SA form I	4BRBZ:AA	4BRBZ:PA	4BRBZ:SUA	4BRBZ:SBA	4BRBZ:FA form II	4BRBZ:SA form II	4BRBZ form I	4BRBZ form II
formula	$2(C_7H_6BrNO)\cdot(C_3H_4O_4)$	$2(C_7H_6BrNO)\cdot(C_4H_4O_4)$	$(C_7H_6BrNO)\cdot 0.5(C_4H_6O_4)$	$(C_7H_6BrNO)\cdot 0.5(C_6H_{10}O_4)$	$(C_7H_6BrNO)\cdot 0.5(C_7H_{12}O_4)$	$(C_7H_6BrNO)\cdot 0.5(C_8H_{14}O_4)$	$(C_7H_6BrNO)\cdot 0.5(C_{10}H_{18}O_4)$	$4(C_7H_6BrO)\cdot(C_4H_4O_4)$	$4(C_7H_6BrNO)\cdot(C_4H_6O_4)$	(C_7H_6BrNO)	(C_7H_6BrNO)
formula weight	504.12	516.13	259.07	273.10	280.11	287.13	301.15	916.18	918.20	200.03	200.03
crystal system	monoclinic	monoclinic	triclinic	triclinic	monoclinic	triclinic	triclinic	monoclinic	monoclinic	triclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$C2/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P2_1/c$
a (Å)	10.3130(15)	9.381(7)	6.4642(15)	5.0396(7)	17.124(12)	5.0254(7)	5.0640(6)	12.7670(9)	12.9755(9)	5.061(8)	4.922(4)
b (Å)	4.9411(7)	10.207(7)	7.2290(17)	8.3137(12)	5.017(3)	9.4144(13)	8.3509(10)	21.9607(16)	21.9158(14)	7.103(12)	5.349(4)
c (Å)	37.823(5)	20.488(14)	11.086(3)	13.5905(19)	27.220(19)	13.4916(19)	16.0318(19)	12.2349(9)	12.3156(8)	11.055(18)	27.65(2)
α (°)	90	90	99.922(8)	82.040(6)	90	103.538(7)	101.986(7)	90	90	103.913(19)	90
β (°)	95.081(6)	99.286(9)	106.921(5)	89.031(6)	101.934(19)	100.547(6)	90.873(6)	102.520(7)	103.567(7)	95.87(2)	93.501(9)
γ (°)	90	90	91.202(6)	74.017(5)	90	104.493(5)	105.479(7)	90	90	103.151(16)	90
V (Å^3)	1919.8(5)	1936(2)	486.8(2)	541.99(13)	2288(3)	580.69(14)	637.33(13)	3348.8(4)	3404.5(4)	370.4(10)	726.6(10)
Z	4	4	2	2	8	2	2	4	4	2	4
ρ calc (g cm^{-3})	1.744	1.771	1.768	1.673	1.626	1.642	1.569	1.817	1.791	1.794	1.829
$F(000)$	1000.0	1024.0	258.0	274.0	1128.0	290.0	306.0	1808.0	1816.0	196.0	392.0
μ (mm^{-1})	4.259	4.225	4.201	3.778	3.582	3.531	3.221	4.864	4.785	5.473	5.580
temp (K)	150	150	150	150	150	150	150	150	150	150	150
total ref	13702	19523	5076	5769	11084	6244	6841	35208	35940	3848	5642
unique ref	4363	4442	2250	2484	2636	2671	2920	7662	7789	1668	1674
observed ref $[I > 2\sigma(I)]$	3418	3665	1824	2028	2242	2360	2611	5917	5799	1137	1395
R	0.0762	0.0603	0.0322	0.0407	0.0628	0.0333	0.0303	0.0411	0.0430	0.0759	0.0490
wR2	0.2401	0.1695	0.0855	0.0897	0.1710	0.0755	0.0720	0.0932	0.0883	0.2100	0.1643
S	1.092	1.093	1.039	1.048	1.061	1.064	1.066	1.040	1.030	0.954	1.099
CCDC no.	933460	926805	926806	926807	926808	926809	926810	926811	926812	933461	933462

[a]4BRBZ, 4-Bromobenzamide; MA, malonic acid; FA, fumaric acid; SA, succinic acid; AA, adipic acid; PA, pimelic acid; SUB, suberic acid; SBA, sebacic acid.

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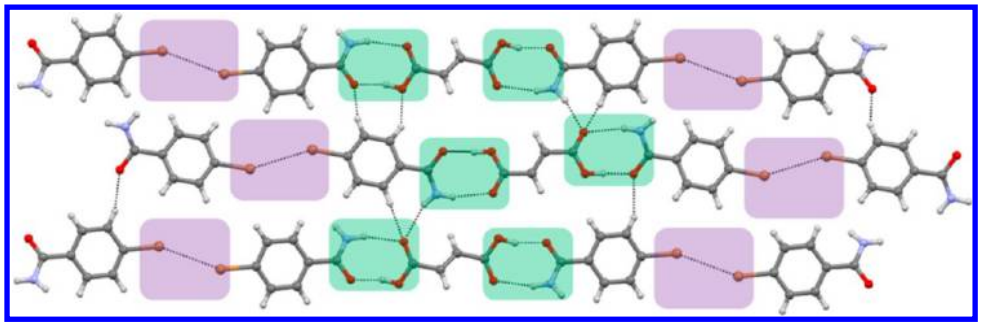

Figure 6. 4-Bromobenzamide:fumaric acid 2:1 cocrystal form I (**2**), built up with acid−amide heterosynthon and Br···Br type I halogen interactions.

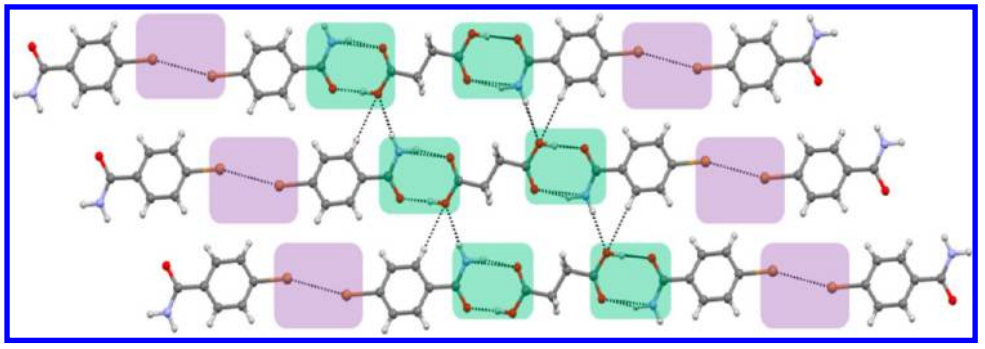

Figure 7. 4-Bromobenzamide:succinic acid 2:1 cocrystal form I (**3**). Packing is stabilized by acid−amide synthons and type I Br···Br interactions. Two adjacent acid−amide heterosynthons are connected with N−H···O and C−H···O interactions.

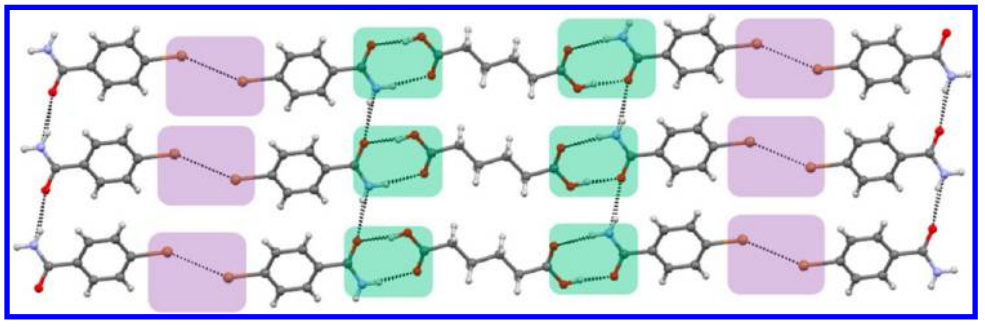

Figure 8. 4-Bromobenzamide:adipic acid 2:1 cocrystal (**4**). Molecules are connected by acid−amide, N−H···O synthons, and type I Br···Br halogen interactions.

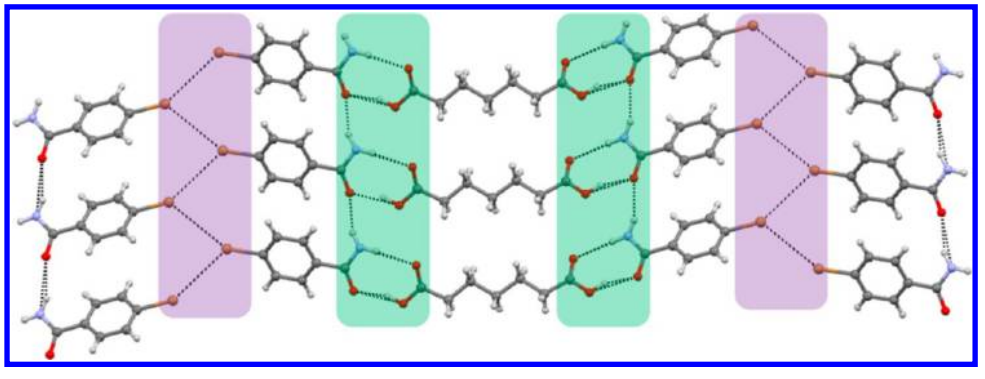

Figure 9. 4-Bromobenzamide:pimelic acid 2:1 cocrystal (**5**). The packing is stabilized by acid−amide heterosynthons and quasi type I halogen interactions. Notice the Br···Br···Br chain similar to the O−H···O−H···O−H··· cooperative infinite hydrogen bond chain in the 4-hydroxybenzamide-dicarboxylic acid cocrystals.

compounds, complete crystallization details are not available (Table 4). The cocrystal architecture in the present study is compatible with both type I and type II interactions. The 2:1 cocrystals formed from the even diacids incorporate a type I Br···Br interaction (Figures 6, 7, 8, 10, and 11). The cocrystals formed by the odd diacids have quasi type I/type II Br···Br contacts (Figures 5 and 9). The 2:1 cocrystals of all the diacids except malonic acid adopt a ladderlike structure (Figure 6, 7, 8,

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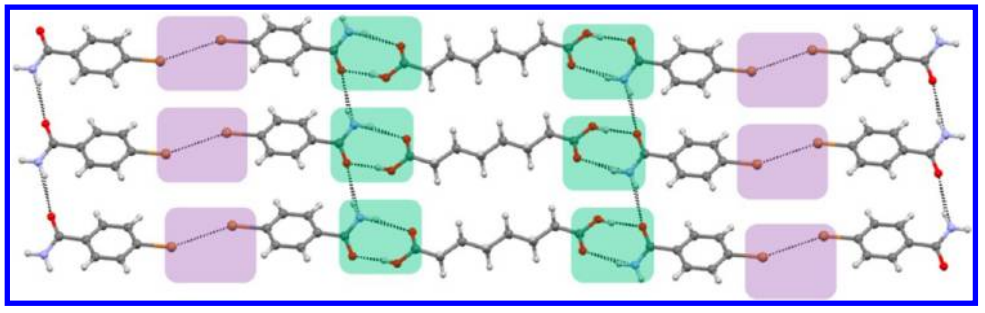

Figure 10. 4-Bromobenzamide:suberic acid 2:1 cocrystal (**6**). Compare this with cocrystals (**3**) and (**4**).

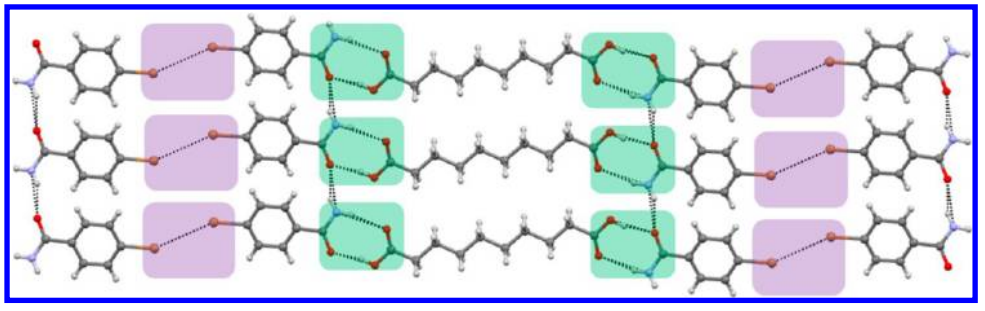

Figure 11. 4-Bromobenzamide:sebacic acid 2:1 cocrystal (**7**). Packing is similar to structures (**3**), (**4**), and (**6**).

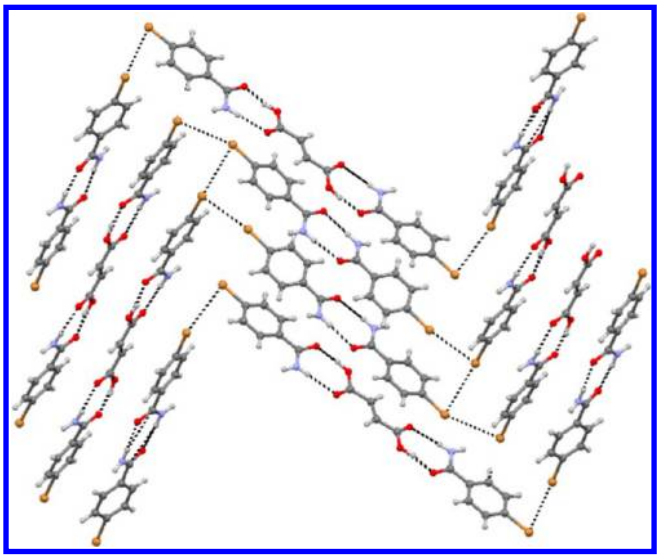

Figure 12. 4-Bromobenzamide:fumaric acid 4:1 cocrystal (form II) (**8**). Notice how the amide−amide homosynthon and the three-molecule hydrogen-bonded aggregate are connected with type II halogen interactions.

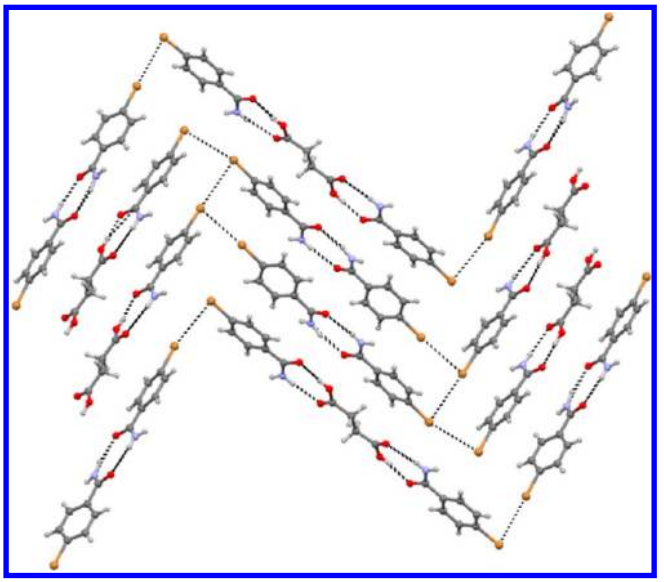

Figure 13. 4-Bromobenzamide:succinic acid 4:1 cocrystal (form II) (**9**). Note the similarity to cocrystal **8**.

9, 10, and 11). In the 4:1 cocrystals of even diacids, aggregates and amide−amide synthons are connected with type II Br···Br interactions (Figures 12 and 13).

Identification of Synthons by IR Spectroscopy. IR spectroscopy can be used for the identification of synthon formation.[30] Very recently, we have disclosed a procedure for the systematic detection of acid−pyridine and amide−amide synthons with IR spectroscopy.[31] The N−H vibrations present in the amide−amide synthon are identified in the region of 3125−3190 (ν_1, symmetric stretching) and 3275−3400 cm^{-1} (ν_2, asymmetric stretching). The IR spectra of 4-bromobenzamide has two vibration bands at 3172 and 3362 cm^{-1}, in agreement with the amide−amide synthon formation. The presence of the acid−amide synthon in cocrystals results in a blue shift of N−H vibrations to a higher frequency (Figure 14), (Table 5). The existence of these systematically shifted bands along with characteristic additional O−H bands is direct evidence for acid−amide heterosynthon formation.[32]

CONCLUSIONS

Cocrystals of 4-bromobenzamide with *n*-alkanedicarboxylic acids contain acid−amide synthons and Br···Br interactions, which include type I, type II, and quasi type I/type II. Suggested angular ranges for these types of $X_1\cdots X_2$ interactions ($X_1 = X_2$) are given. In I···I contacts, a clear distinction is observed between type I and type II contacts. The distribution of types I and II over a distance, ranging to van der Waals radius +0.05 Å, shows that type II interactions are viable at long distances in keeping with their electrostatic nature. On the

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Table 4. Polymorphism Based on Differences in the Br···Br Interaction (Type I and II)

compound	refcode	space group	Br···Br	θ_1 (deg)	θ_2 (deg)	Br···Br (Å)	density	remarks
1,4-bis(tribromomethyl) benzene	YADKUL01[23]	$C2/c$	type II	154.2	94.5	3.580	3.080	concomitantly from $CDCl_3$ but form II (type I) is of the "disappearing" variety
	YADKUL[23]	$P2_1/n$	type I	139.6	139.6	3.698	3.165	
4-bromonitrosobenzene	XAJPII[24a]	$P\bar{1}$	type I	176.6	176.6	3.136	1.934	sublimation under pressure
	XAJPII01[24b]	$P2_1$	quasi type I/II	158.3	131.8	3.695	2.008	in situ irradiation of dimer with Hg lamp in a stream of liquid N_2 at 100 K
tri-*O*-*p*-bromo-benzoyl-*myo*-inositol 1,3,5-orthoformate	VEBBUA[25]	$C2/c$	quasi type I/II	156.6	139.7	3.404	1.862	concomitantly from EtOAc-petroleum ether, but form I (type II) is kinetically stable, while form II (type I) is thermodynamically stable
	VEBBUA01[25]	$P\bar{1}$	type I	153.8	153.8	3.444	1.758	
3,6,13,16-tetra-bromo-2,7,12,17-tetra-*n*-propylporphycene	KIJGUF[26a]	$P\bar{1}$	type I	147.3	147.3	3.418	1.670	concomitantly from CH_2Cl_2-*n*-hexane
	KIJGUF01[26b]	$P2_1/c$	type II	160.8	123.1	3.671	1.731	
	KIJGUF02[26c]	$P2_1/n$	quasi type I/II	139.7	121.3	3.678	1.734	
tetrakis(2-bromoethyl)methane	EABVEI[27]	$P42c$	type I	141.3	141.3	3.608	2.143	from EtOH
	EABVEI01	$P2_12_12_1$	type II	168.9	112.9	3.506	2.238	private communication
4-bromophenylboronic acid	BPHBAC[28a]	$P6/mcc$	type II	170.4	69.6	3.406	1.720	crystallization details not available
	BPHBAC01[28b]	$P\bar{1}$	type I	164.7	164.7	3.567	1.775	from water
cis-9,10-bis(4-bromophenyl)-9,10-dihydroxy-9,10-dihydroanthracene	QODQUV[29]	Cc	type II	159.0	85.1	3.699	1.652	from toluene and a trace of $CHCl_3$
	QODQUV01[29]	$P\bar{1}$	type I	155.1	155.1	3.398	1.645	from toluene
4-bromobenzamide	BBEZAM[21a]	$P\bar{1}$	type I	165.8	165.8	3.488	1.794	concomitantly from THF
	BBEZAM01[21b]	$P2_1/a$	type II	170.1	91.8	3.639	1.829	

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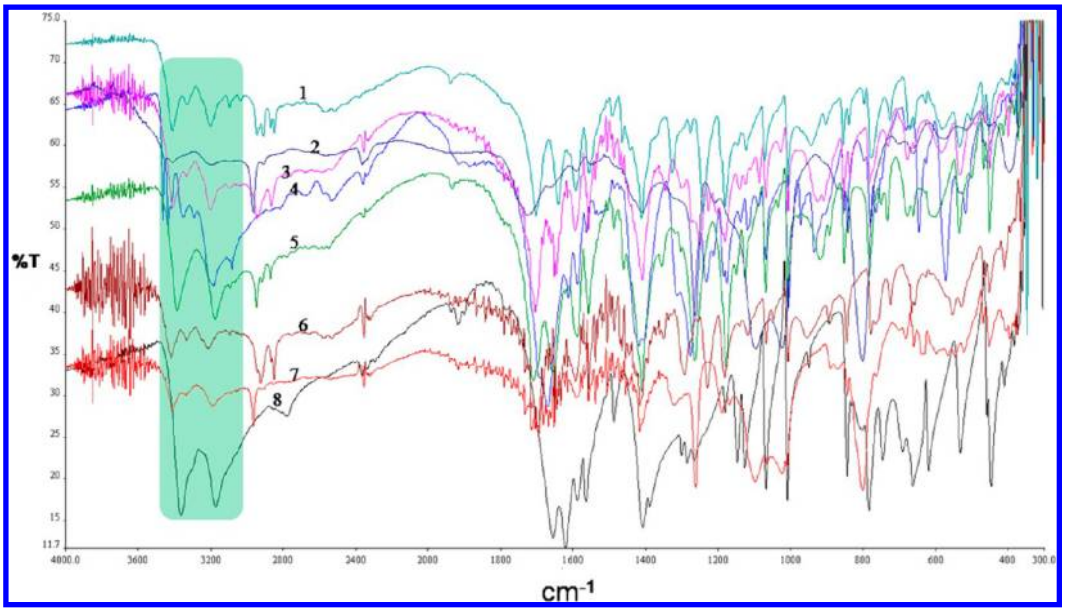

Figure 14. IR spectra of 4-bromobenzamide:dicarboxylic acid cocrystals. (1) 4-Bromobenzamide:suberic acid, (2) 4-bromobenzamide:malonic acid, (3) 4-bromobenzamide:pimelic acid, (4) 4-bromobenzamide:fumaric acid, (5) 4-bromobenzamide:adipic acid, (6) 4-bromobenzamide:sebacic acid, (7) 4-bromobenzamide:succinic acid, and (8) 4-bromobenzamide.

Table 5. IR Spectra of 4-Bromobenzamide:Dicarboxylic Acid Cocrystals

	cocrystals	wave number ν_2 (cm^{-1})	wave number ν_1 (cm^{-1})
1	4-bromobenzamide:suberic acid	3411	3201
2	4-bromobenzamide:malonic acid	3408	3200
3	4-bromobenzamide:pimelic acid	3407	3202
4	4-bromobenzamide:fumaric acid	3434	3183
5	4-bromobenzamide:adipic acid	3384	3175
6	4-bromobenzamide:sebacic acid	3418	3218
7	4-bromobenzamide:succinic acid	3409	3191
8	4-bromobenzamide	3362	3172

other hand, type I interactions are prominent at short distances. In all the cocrystals, the dicarboxylic acids are inserted between the amide−amide homodimer of the 4-bromobenzamide crystal. A selective incorporation of Br···Br type I contacts is observed in 2:1 cocrystals formed from even diacids. The 2:1 cocrystals from odd diacids have quasi type I Br···Br interactions. The 4:1 cocrystals of even diacids consist of aggregates, which are connected with type II Br···Br interactions. IR spectroscopy is useful in the identification of acid−amide heterosynthons.

■ ASSOCIATED CONTENT

Supporting Information

PXRD pattern of 4-bromobenzamide−oxalic acid, HSM images of 4-bromobenzamide−oxalic acid cocrystals at different temperatures, ORTEP diagrams of all crystals, and SHELXL-97 data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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