Halogen Bond Motifs in Cocrystals of \(N,N,O\) and \(N,O,O\) Acceptors Derived from Diketones and Containing a Morpholine or Piperazine Moiety

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ABSTRACT: In this study, we investigate the halogen bond acceptor potential of oxygen and nitrogen atoms of morpholine and piperazine fragments when they are peripherally located on \(N,O,O\) or \(N,N,O\) acceptor molecules. We synthesized four acceptor molecules derived from either acetylacetone or benzoylacetone and cocrystallized them with 1,4-diiodotetrafluorobenzene and 1,3,5-triiodotrifluorobenzene. This resulted in eight cocrystals featuring halogen bonds. The \(N\) and \(O\) halogen bond acceptor sites were evaluated through calculations of molecular electrostatic potential values.

In the last three decades, the halogen bond has become recognized as a valuable tool in crystal engineering.

Because of its larger directionality (as compared to the hydrogen bond), tunability achievable by changing the donor halogen atom in otherwise structurally equivalent donor molecules, the halogen bond found its way into a rising number of scientific studies on the synthesis and design of functional materials as well as organic synthesis, solution chemistry, pharmaceutical, and theoretical chemistry.

The list of studied halogen bond donors and especially halogen bond acceptors grows continuously. Cyclic nitrogen atoms are the most studied and reliable acceptor species, and this is especially the case for pyridine nitrogen atoms, to the point that they are a valuable benchmark for donor evaluation and studies on acceptor competitiveness.

In recent years, they have been followed by a variety of other, mostly nitrogen or oxygen atom containing species, such as methoxy, nitro, hydroxyl, and nitrite functional groups, and oxygen atoms in N-oxides. Some recent studies also showcased the promising halogen bond acceptor potential of nitrogen atoms in piperazine and nitrogen and oxygen atoms in morpholine as well as the carbonyl oxygen atom. So far, systematic studies of halogen bonding with these moieties were mainly limited to smaller building blocks. Searching the Cambridge Structural Database, one can find a small number of larger, relatively bulky building blocks that are halogen bonded via either the morpholine oxygen or piperazine nitrogen atoms. Most numerous are polyfunctional organic compounds, followed by metal–organic complexes and clathrates. Only a few of these studies have been systematically focused on halogen bonding. Therefore, we set out to further investigate the possibility of halogen bond formation and the possible diversity of halogen bond motifs in bulkier molecules containing peripherally located morpholine and piperazine fragments as potential building blocks in the design of novel halogen-bonded multicomponent solids.

In this work, four novel Schiff bases (BM, BP, AM, AP; see Scheme 1) were synthesized by a condensation reaction from two diketones, benzoylecetone (B) and acetylacetone (A), and two primary amines, \(N\)-(2-aminoethyl)morpholine (M) and \(N\)-(2-aminoethyl)piperazine (P). Single crystals and solid bulk of pure acceptors were obtained only in the case of BM. Each of these molecules has three potential halogen bond acceptor sites: the carbonyl oxygen atom, nitrogen and oxygen atoms in the morpholine fragment, and the two nitrogen atoms in the piperazine fragment. An additional secondary amine nitrogen atom is also present in each of
these acceptors; however, because of the geometric disposition of bonded atoms and its basicity (in comparison with the other sites, see above), this atom is not an expected acceptor site. As halogen bond donors, we selected two perfluorinated aromatic halogen bond (XB) donors, 1,4-diiodotetrafluorobenzene (14tfib) as a linear ditopic donor and 1,3,5-triodo-2,4,6-trifluorobenzene (135tfib) as a potentially tritopic donor (Scheme 1).

For the purpose of ranking the acceptor sites in the acceptor molecules used in this work, the values of molecular electrostatic potentials (MEPs) were calculated on their optimized geometries (Figure 1).

Minima on the potential energy surfaces (PES) of the acceptors AM and AP correspond to the bent conformations, in which only two acceptor sites are available for halogen bonding. In both molecules, the MEP value on the keto oxygen atom is more negative than that on either the morpholine oxygen atom in AM or the piperazine nitrogen atoms in AP. In the case of AP, this difference is somewhat less pronounced, reflecting the potentially higher acceptor strength of the piperazine nitrogen atom in AP, compared to the morpholine oxygen atom present in AM (ΔMEP(AP) = 35 kJ mol⁻¹ e⁻¹, ΔMEP(AP) = 40 kJ mol⁻¹ e⁻¹). Optimization of the extended conformation of the AP molecule which can be found in the (AP)(135tfib) cocrystal (see below) resulted in a geometry which corresponds to a local minimum and contains an additional acceptor site (the tertiary piperazine nitrogen atom). On the absolute scale, the MEP value of the tertiary piperazine nitrogen atom is the lowest one in the AP molecule and indicates the poor halogen bond acceptor strength of this moiety. After optimization, BM and BP molecules are in extended conformations, and they consequently contain three acceptor sites. On the basis of the calculated MEPs, in both molecules the best acceptor species is the keto oxygen atom, followed by either the morpholine oxygen atom (in BM) or the piperazine nitrogen atom (in BP), while the secondary amine nitrogen has been expectedly found as the weakest halogen bond acceptor site in those molecules.

Cocrystallization experiments were performed by dissolving XB donors in acceptor solutions made in an appropriate solvent or a mixture of solvents. Crystallization vessels were...
of eight new halogen-bonded cocrystals were obtained: (BM)\(_{(14tfib)}\), (BM)\(_{(135tfib)}\), (BP)\(_{(14tfib)}\), and (BP)\(_{(135tfib)}\). The obtained products were characterized by single-crystal X-ray diffraction (SCXRD), Fourier-transform infrared spectroscopy (FTIR), and thermal analysis techniques (TG – DSC). A total of eight new halogen-bonded cocrystals were obtained: (BM)\(_{(14tfib)}\), (BM)\(_{(135tfib)}\), (BP)\(_{(14tfib)}\), (BP)\(_{(135tfib)}\), (AM)\(_{(14tfib)}\), (AM)\(_{(135tfib)}\), (AP)\(_{(14tfib)}\), and (AP)\(_{(135tfib)}\) (Table 1). From the crystallographic data presented in Table 1, it is noticeable that the most prominent halogen bond is the one with the terminal piperazine nitrogen atom, is present in all four obtained piperazine building block cocrystals, and features the largest relative shortening values (from 16.4% to 22.9% and averaging at 19.8%). It is followed by the I···O carbonyl halogen bond, present in seven out of eight obtained cocrystals, with relative shortening values ranging from 14.4% to 20.0% and averaging at 17.5%. These R.S. values indicate that halogen bonds of this type can be classified as fairly strong. It can be observed that the carbonyl oxygen atom in all crystal structures forms slightly longer halogen bonds than the piperazine nitrogen atom, even though calculated MEP values on the carbonyl oxygen atoms are for the most part more negative than those on piperazine nitrogen atoms. These observed “deviations” in relative shortening values can be explained by lower steric constraints and consequently greater spatial availability of the terminal nitrogen atom relative to the carbonyl oxygen. This is especially the case in cocrystals where the acceptor molecule is in a bent conformation. Contrary to expectations based on our previous work, the I···O morpholine halogen bond, although present in all four morpholine building block cocrystals, has the lowest relative shortening values, ranging between 7.3% and 15.7% and averaging at 12.9%. Somewhat stronger I···N morpholine halogen bonds are present in three out of four morpholine building block cocrystals, with an average R.S. of 14.0%. The (AM)\(_{(14tfib)}\) cocrystal is the only one that does not contain an I···N morpholine halogen bond.

In all cocrystals in which it is present, 14tfib acts as a linear ditopic donor, while 135tfib, as expected due to its three donor atoms placed at an angle, forms structurally more

| cocrystal          | D···A     | acceptor moiety          | d(D···A)/Å | R.S.\(^a\)/% | \(\angle(C\cdots D\cdots A)/^\circ\) |
|--------------------|----------|--------------------------|-----------|---------------|----------------------------------|
| (BM)\(_{(14tfib)}\) | 11···O1   | carbonyl                 | 2.879     | 17.7          | 177.3                           |
|                    | 12···O2   | morpholine               | 2.950     | 15.7          | 197.8                           |
|                    | 13···N2   | morpholine               | 3.035     | 14.0          | 196.7                           |
| (BM)\(_{(135tfib)}\) | 11···O1   | carbonyl                 | 2.977     | 14.4          | 175.3                           |
|                    | 14···N2   | morpholine               | 3.008     | 14.8          | 165.9                           |
|                    | 15···O2   | morpholine               | 3.243     | 7.3           | 143.3                           |
| (BP)\(_{(14tfib)}\)  | 12···N2   | proximal piperazine      | 2.948     | 16.5          | 176.5                           |
|                    | 11···N3   | terminal piperazine      | 2.760     | 21.8          | 177.3                           |
| (BP)\(_{(135tfib)}\) | 11···O1   | carbonyl                 | 2.917     | 16.7          | 173.6                           |
|                    | 17···N2   | proximal piperazine      | 2.984     | 15.5          | 171.6                           |
|                    | 14···N3   | terminal piperazine      | 2.948     | 16.5          | 171.1                           |
|                    | 12···O2   | carbonyl                 | 2.931     | 16.3          | 171.5                           |
|                    | 15···N5   | proximal piperazine      | 2.961     | 16.1          | 173.5                           |
|                    | 18···N6   | terminal piperazine      | 2.953     | 16.4          | 167.0                           |
| (AM)\(_{(14tfib)}\)  | 11···O1   | carbonyl                 | 2.800     | 20.0          | 174.1                           |
|                    | 12···O2   | morpholine               | 3.015     | 13.9          | 177.5                           |
| (AM)\(_{(135tfib)}\) | 12···O1   | carbonyl                 | 2.972     | 15.1          | 173.1                           |
|                    | 14···O2   | morpholine               | 3.062     | 12.5          | 168.6                           |
|                    | 15···N2   | morpholine               | 3.119     | 11.6          | 173.4                           |
|                    | 110···O3  | carbonyl                 | 2.846     | 18.7          | 174.8                           |
|                    | 19···O4   | morpholine               | 2.979     | 14.9          | 165.7                           |
|                    | 17···N4   | morpholine               | 2.981     | 15.6          | 173.6                           |
| (AP)\(_{(14tfib)}\)  | 11···N3   | terminal piperazine      | 2.721     | 22.9          | 176.8                           |
|                    | 12···O1   | carbonyl                 | 2.810     | 19.7          | 178.8                           |
| (AP)\(_{(135tfib)}\) | 11···N3   | terminal piperazine      | 2.779     | 21.3          | 176.4                           |
|                    | 13···O1   | carbonyl                 | 2.846     | 18.7          | 178.2                           |
|                    | 11···I2   | 135tfib                  | 3.959     | 0.03          | 163.5                           |

\(^{a}\)R.S. = 1 – d(D···A)/\([r_{vdW}(D) + r_{vdW}(A)]\).
intricate and diverse halogen bond motifs. Discrete halogen-bonded complexes are formed in three cocrystals with the sterically more flexible AM and AP molecules, (AM)(14tfib), (AP)(14tfib), and (AP)(135tfib), since the acceptor molecules can bend and adjust the position of their acceptor sites (Figure 3). In these cocrystals, the acceptor and donor molecules are interconnected by a combination of I⋯O_carbonyl and I⋯O_morpholine or I⋯N_piperazine halogen bonds, respectively. In the (AM)(14tfib) and (AP)(14tfib) cocrystals, the discrete complexes are connected into 3D by van der Waals contacts, while in (AP)(135tfib) they are further connected into chains via C−H⋯F and I⋯I contacts (Figure 4).

In cocrystals with the more sterically hindered BM and BP molecules, acceptors are connected by one or more symmetrically inequivalent halogen bond donor molecules into halogen-bonded chains. In (BM)₂(14tfib)₅, pairs of acceptor molecules are bridged by three 14tfib molecules (Figure 5). A symmetrically inequivalent, nonbridging 14tfib molecule participates in a weak I⋯π(C=C) halogen bond.

Figure 3. Discrete halogen-bonded complexes in crystal structures of (a) (AM)(14tfib), (b) (AP)(14tfib), and (c) (AP)(135tfib).

Figure 4. Fragments of halogen- and hydrogen-bonded chains in crystal structures of (a) (AM)(14tfib), (b) (AP)(14tfib), and (c) (AP)(135tfib). Halogen bonds (I⋯O and I⋯N) are orange, hydrogen bonds are green, and I⋯I halogen bonds are blue.

Figure 5. Halogen-bonded chains of (BM)₂(14tfib)₅.
These chains are further connected into layers by with weak I⋯π(C≡C) halogen bonds and C−H⋯O_{carbonyl} and C−H⋯π\{(phenyl)\} hydrogen bonds. The layers are expanded in 3D via weak C−H⋯F contacts.

In \((BM)(135t\text{fib})_2\), acceptor molecules are bridged by two symmetrically inequivalent \(135t\text{fib}\) molecules: one is halogen bonded to a morpholine oxygen atom and a morpholine nitrogen atom on an adjacent acceptor molecule, while the other \(135t\text{fib}\) molecule is halogen bonded to the carboxyl oxygen atom and participates in weak I⋯π(C≡C) interactions with another acceptor molecule. The same halogen-bonding motifs can be observed in \((BP)(14t\text{fib})\) and \((AM)(135t\text{fib})_2\) cocrystals (Figure 6).

In \((BP)(14t\text{fib})\), the only herein presented cocrystal that does not contain halogen-bonded oxygen atoms, zigzag halogen-bonded chains are formed, in which \(14t\text{fib}\) molecules alternate in bridging proximal and terminal piperazine nitrogen atoms (Figure 7). The resulting chains are connected into layers through N−H⋯O hydrogen bonds, with the layers then connected into 3D by weak C−H⋯F interactions.

Melting points of all of the obtained cocrystals were determined using TG-DSC analysis. For the purposes of thermal analysis, crystal bulks were synthesized by dissolving the reactants in the ratio obtained from single-crystal data. The measured PXRD patterns for the crystal bulks were found to be in good agreement with the patterns calculated from single-crystal data. Thermal analysis results are shown in Table S2 (see Supporting Information). With an exception in the \((BP)(14t\text{fib})\) cocrystal, which decomposes, all other cocrystals feature melting points as evidenced by a comparison of TG and DSC curves. Contrary to expectations, the melting point of the \((BM)_2(14t\text{fib})_5\) cocrystal is the lowest of all, even though BM is the only acceptor obtained in the solid state. Otherwise, BM and BP cocrystals feature higher melting and decomposition point temperatures than AM and AP cocrystals.

To conclude, following our previous course of research, we have confirmed the potential of morpholine and piperazine nitrogen and oxygen atoms, as well as the carbonyl oxygen atom, as halogen bond acceptors in larger molecular building blocks by synthesizing eight cocrystals. Both the morpholinyl oxygen atom and terminal piperazine nitrogen atom were found to act as halogen bond acceptor sites in all herein.
presented cocrystals. However, from our analysis of crystallographic data and the comparison between relative shortening values, it is possible to infer that the terminal piperazine nitrogen atom is a better halogen bond acceptor site than the morpholinyl oxygen atom. These results could open up interesting pathways in the further development of strategies for designing novel halogen-bonded multicomponent solids, though additional studies of these bonding motifs should be performed to ascertain their reliability.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd.2c00665.

Experimental and computational details, including TG-DSC curves, PXRD patterns and single-crystal diffraction data (PDF)

**Accession Codes**

CCDC 2176816–2176824 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**Notes**

The authors declare no competing financial interest.

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