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Arun Dhaka, Olivier Jeannin, Emmanuel Aubert, Enrique Espinosa, Marc Fourmigué, et al.. N-Chlorobenzimidazoles as efficient and structurally diverse amphoteric halogen bond donors in crystal engineering. *Chemical Communications*, 2022, 58 (77), pp.10825-10828. 10.1039/d2cc03971k . hal-03797315

HAL Id: hal-03797315

<https://hal.science/hal-03797315>

Submitted on 18 Nov 2022

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N-chlorobenzimidazoles as efficient and structurally diverse amphoteric halogen bond donors in crystal engineering†

Received 00th January 20xx,
Accepted 00th January 20xx

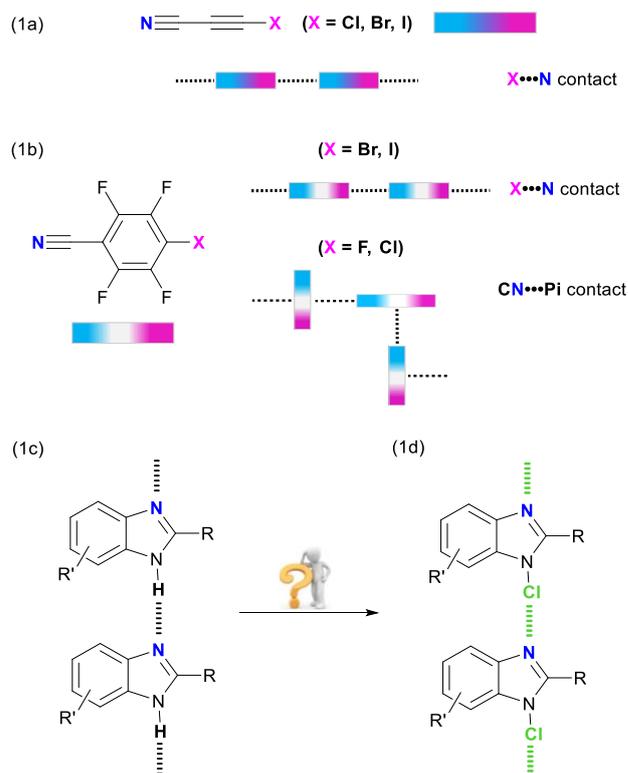
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DOI: 10.1039/x0xx00000x

The ability of amphoteric N-chlorobenzimidazoles to self-associate into 1D chains through strong and linear N–Cl•••N halogen bond interactions is demonstrated. Less polarisable Cl atom is strongly activated thanks to the intramolecular amphoteric character and the intermolecular cooperativity effect. The obtained family of compounds featuring different substitution patterns opens perspectives toward the elaboration of macroscopic polar structures.

During the past decades, the development of molecular solids with new applications has been achieved through supramolecular approaches that rely on our understanding of intermolecular interactions^{1,2} i.e. hydrogen bond.³ In this context, the halogen bond (XB)⁴ has been established as an efficient structuring tool in crystal engineering strategies owing to its advanced fundamental understanding, inherent directionality and most significantly predictability.^{5,6} Strong activation of iodine in classical XB donors like diiodotetrafluorobenzene⁷ and diiodoperfluoroalkanes⁸ allows them to competently participate in co-crystal formation with an electron rich partner. However, difficult activation of a sigma-hole in XB donors involving rather less polarizable halogen atoms find limited use of lighter elements i.e. $F < Cl \ll Br$ in supramolecular synthesis. On the other hand, molecular assemblies recognized through self-association ability, require a self-complementary system bearing both an activated donor and an acceptor site.^{9,10} Such amphoteric molecules for XB remain limited, which might be attributed to the difficult integration of donor and acceptor sites in a molecule at a desired position. For instance, linear X-cyanoacetylene were demonstrated to organize into infinite 1D chains through short $X \cdots N$ contacts with distances 2.970, 2.956, and 2.930 Å respectively for $X = Cl, Br, \text{ and } I$ (Scheme 1a).^{11–13} Crystal structure of a neutral diaryl-5-iodo-1,2,3-triazole was shown to exhibit an antiparallel arrangement of molecular tapes formed through $I \cdots N$ contacts.¹⁴ Moreover, examples of self-associating XB donors

resulting into a dimeric^{15–17} and trimeric^{18–20} structures in the solid-state are also known. A self-complementary system that features structural diversity is of importance as it allows us to induce the structural polarity in the solid-state. For example, moving from $X-C \equiv C-CN$ to perfluorinated $X-C_6F_4-CN$ based system promoted a reduced interaction between the XB bonded 1D chains that favoured a co-parallel/non-centrosymmetric arrangement



Scheme 1 Literature examples of self-associating XB 1D systems (1a & 1b). Hydrogen bonding in benzimidazoles leading to 1D polar chains (1c), and halogen bonding in N-chlorobenzimidazoles illustrated in this work (1d).

over an antiparallel/centrosymmetric arrangement.²¹ Interestingly, $X-C_6F_4-CN$ ($X = I, Br$) resulted into 1D chain motif through $X \cdots N$ contacts whereas $X-C_6F_4-CN$ ($X = F, Cl$) crystallized differently favouring $CN \cdots \pi$ interactions (Scheme 1b). This example indeed

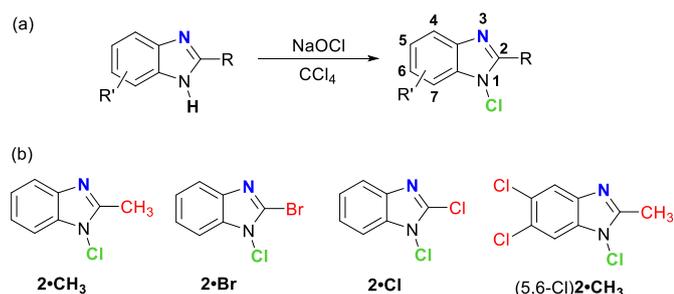
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†Electronic Supplementary Information (ESI) available: Experimental details, NMR spectra, crystallographic data, theoretical calculation details, additional structure figures, and crystallographic information files (CIF). CCDC 2173224–2173227. See DOI: 10.1039/x0xx00000x

elegantly demonstrates the tendency of lighter halogen atoms to involve into interactions that are less structure directing. Therefore, use of XB based self-associating systems in crystal engineering strategies, especially those involving lighter halogen atoms ($X = F, Cl$) remains very challenging. This can be attributed to the more demanding activation of a sigma-hole on highly electronegative atoms as well as the synthetic complexity or chemical instability of such systems.

Benzimidazole derivatives bearing both hydrogen bond donor and acceptor sites were recently reported to systematically self-associate into hydrogen bonded polar chains (Scheme 1c).²² Inspired from this work, we considered replacing the N–H with N–Cl functionality anticipating that activation of a strong sigma-hole on chlorine atom would similarly favour the molecular assembly into halogen bonded polar chains (Scheme 1d). In this manuscript, we report synthesis of structurally diverse N-chlorobenzimidazole derivatives that upon crystallization self-assemble into the sought after XB bonded polar chains though linear and short N–Cl \cdots N contacts. Calculation of electrostatic potential (ESP) in a series of N-chlorobenzimidazole derivatives (Fig. S3) revealed presence of a strong electron depletion on the Cl atom and an electron concentration on the nucleophilic N atom (see Table 1). This indeed confirm a favourable self-association ability of our system.



Scheme 2 Synthesis strategy with atom numbering (a) and N-chlorobenzimidazole derivatives synthesized in this study (b).

Following a reported procedure,²³ functionalization by chlorine was achieved in a single step by treating commercially available benzimidazoles with sodium hypochlorite (NaOCl) solution (Scheme 2) to afford a white crystalline powder of N-chloro-2-methylbenzimidazole (**2•CH₃**), N-chloro-2-bromobenzimidazole (**2•Br**), N-chloro-2-mchlorobenzimidazole (**2•Cl**), and N-chloro-5,6-dichloro-2-methylbenzimidazole ((5,6-Cl)**2•CH₃**) in moderate yields (30–60%). Slow evaporation of ethyl acetate solution containing these newly synthesized derivatives yielded colourless crystals. To our surprise, the only known crystal structure for N-chlorobenzimidazole is 1-chlorobenzimidazole itself ($R = R' = H$), albeit incorrect.¹⁹ The structure was reported indeed with an extra H atom on the sp^2 N3 atom of the heterocycle.

Compound **2•CH₃** crystallizes in the monoclinic system, a centrosymmetric space group $P2_1/c$ with each molecule situated in general position (Fig. S1a). Moreover, we observed an antiparallel arrangement of XB chains that are primarily driven by strong

electrophilic \cdots nucleophilic interactions with a Cl \cdots N distance of 2.648 Å, corresponding to a reduction ratio (RR) of 0.80 relative to the sum of their van der Waals radii (Fig. 1). The XB directionality in this motif is manifested by a highly linear Cl \cdots N contact with $\angle N_D\text{--}Cl\cdots N_A = 176.3^\circ$ (Table 1). These structural details indeed highlight the excellent ability of systematic self-association driven by Cl \cdots N XB interactions. Apart from that, we also observe that these XB chains running in the opposite direction are interconnected through secondary intermolecular interactions such as C–H \cdots N and $\pi\cdots\pi$ interactions (Fig. S1b).

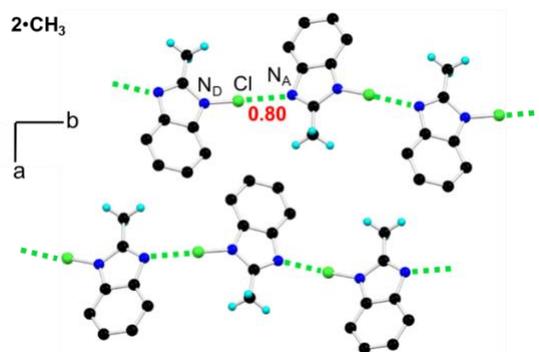


Fig. 1 Solid-state arrangement of **2•CH₃** with antiparallel arrangement of XB chains. The XB motif (RR = 0.80) is shown in green dotted lines. Hydrogens on the phenyl ring have been omitted for clarity.

Table 1 ESP values and solid-state structural details of N-chlorobenzimidazoles. Units: $V_{S,max}$, $V_{S,min}$ and $\Delta V = V_{S,max} - V_{S,min}$ in kcal/mol, angle ($N_D\text{--}Cl\cdots N_A$) in degrees, and RR ($N_A\cdots Cl$) is unit less.

| Compound | $V_{S,max}(Cl)$ | $V_{S,min}(N_A)$ | ΔV | RR | angle |
|--|-----------------|------------------|------------|------|--------|
| 2•CH₃ | +26.41 | –35.39 | 61.8 | 0.80 | 176.31 |
| 2•Br | +29.19 | –33.23 | 62.4 | 0.80 | 176.45 |
| 2•Cl | +29.42 | –33.42 | 62.8 | 0.82 | 172.94 |
| (5,6-Cl)₂•CH₃ | +31.27 | –30.08 | 61.5 | 0.84 | 169.75 |

These benzimidazole-based XB systems offer a large structural diversity that allowed us to think of having different substituents at the imidazole unit (C2 position) as well as on the phenyl ring (C5 and C6 positions). To this end, we synthesized **2•Cl** and **2•Br** derivatives, which crystallize in the monoclinic and the orthorhombic systems, respectively, with space groups $P2_1/c$ and $Pcab$. Their crystal structures revealed a similar centrosymmetric arrangement of XB bonded chains driven through equally short and linear Cl \cdots N contacts (Fig. 2, Table 1).

The Cl atom at C2 position in **2•Cl** does not participate in any interaction and the molecular chains communicate with each other mostly through $\pi\cdots\pi$ interactions (Fig. 3a). Interestingly, the more polarizable Br atom in **2•Br** participates in directional Br $\cdots\pi$

interactions between the neighbouring chains allowing them to organize orthogonal to each other (Fig. 3b).

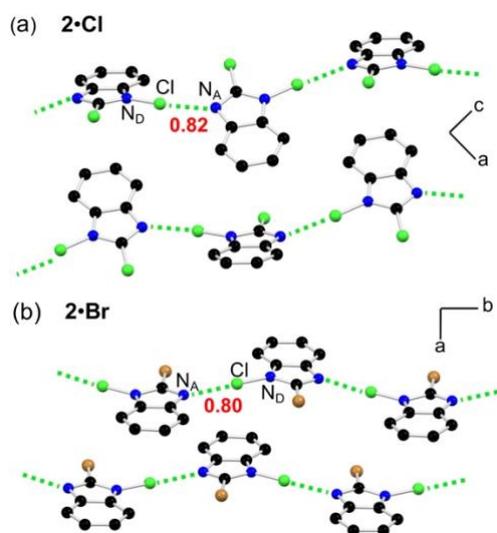


Fig. 2 Molecular arrangement with antiparallel arrangement of XB chains in $2\cdot\text{Cl}$ (a) $2\cdot\text{Br}$ (b). The XB motifs ($RR = 0.81$ and 0.80) are shown in green dotted lines. Hydrogens on the phenyl rings have been omitted for clarity.

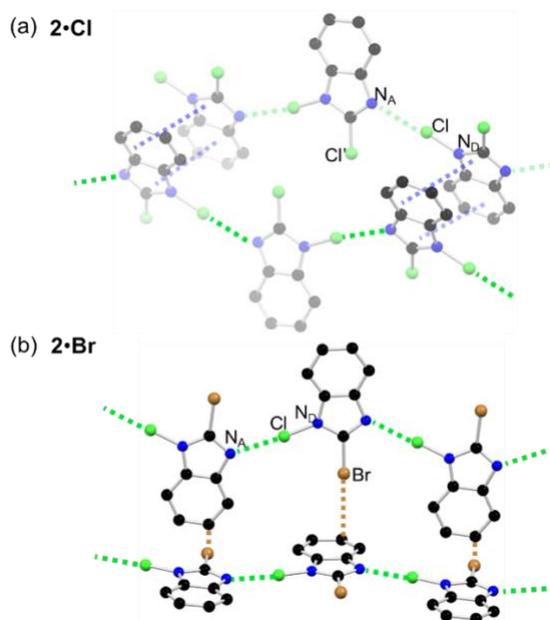


Fig. 3 Secondary intermolecular interactions in crystal structure of $2\cdot\text{Cl}$ exhibiting $\pi\cdots\pi$ interactions (a) and $2\cdot\text{Br}$ exhibiting $\text{Br}\cdots\pi$ interactions (b). Hydrogens on the phenyl rings have been omitted for clarity.

Such recurrent $\text{X}\cdots\pi$ interactions ($\text{X} = \text{Br}, \text{I}$) have been well established in literature that possibly occur when an electrophilic halogen is looking for a partner in the absence of a nucleophilic atom ($\text{N}, \text{O}, \text{S}$ etc).^{24,25} Overall, these results further prove the robust nature of $\text{Cl}\cdots\text{N}$ contacts observed in the different derivatives of N-

chlorobenzimidazole that strongly promote their systematic self-association.

This motivated us to now investigate the effect of possible substituents present on the phenyl ring. Therefore, we synthesized $(5,6\text{-Cl})2\cdot\text{CH}_3$ that has two chlorine atoms positioned in a symmetrical manner at C5 and C6 of the phenyl ring. As shown in Figure 4, the structure reveals a similar antiparallel arrangement of XB molecular chains formed through $\text{Cl}\cdots\text{N}$ contacts of comparable strength ($RR = 0.84$). In this case, the molecular chains communicate with each other through various modes of secondary interactions i.e. weak type-I $\text{Cl}\cdots\text{Cl}$ contacts, $\text{Cl}\cdots\text{H}$ and $\pi\cdots\pi$ interactions (Fig. S2). It is evident that structural diversity in N-chlorobenzimidazole-based system allows us to introduce different interactions between these 1D chains to tune their relative orientation with each other without rupturing the self-association ability. Moreover, the persistent occurrence of $\text{Cl}\cdots\text{N}$ halogen bonds in these derivatives suggests strong activation of a sigma-hole on Cl atom that effectively participate in molecular recognition.

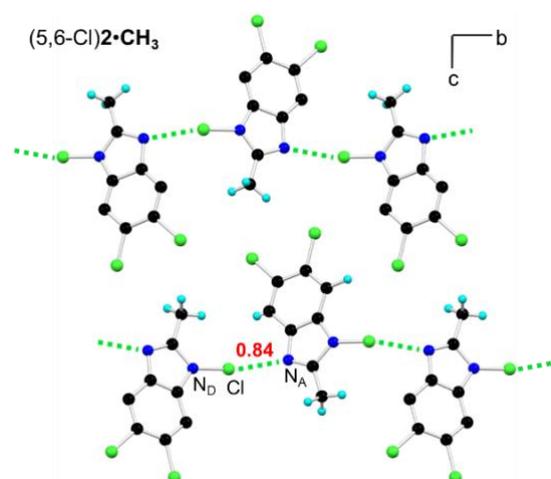


Fig. 4 Molecular arrangement with antiparallel arrangement of dipolar XB chains in $(5,6\text{-Cl})2\cdot\text{CH}_3$. The XB motif ($RR = 0.84$) is shown in green dotted lines. Hydrogens on the phenyl rings have been omitted for clarity.

With these four structures in hand, we took the opportunity to look at the correlation between activation in donor/acceptor and shortening of the $\text{Cl}\cdots\text{N}$ distance (RR). In this series, ESP calculations for isolated molecules in gas phase reveal the weakest activation of Cl ($V_{S,\text{max}}$, Table 1) in $2\cdot\text{CH}_3$ and the strongest in $(5,6\text{-Cl})2\cdot\text{CH}_3$ whereas that of nucleophilic nitrogen ($V_{S,\text{min}}$, Table 1) follow exactly the opposite trend. This is a consequence of electron withdrawing power of different substituents present at C2 or C5/C6 position, i.e. a decrease in the nucleophilic power of N_A/N_D might enhance the electrophilic character of Cl. Moreover, comparable values of RR relate well to similar values of the electrostatic potential difference $\Delta V = V_{S,\text{max}} - V_{S,\text{min}}$, which integrates the permanent electrostatics at both donor and acceptor sites in monomers (Table 1).

To have a further insight on strong activation of N_D-chlorine atom in this family, we compared the electrostatic potential values of halogen atoms on other positions as well. As can be seen from Table S2 and Figure S3, the sigma-hole of chlorine at N_D position is strongly activated compared to the C2-chlorine (+87% increase), whereas the chlorine atoms at positions C5 and C6 are strongly deactivated. Moreover, C2-bromine atom is more polarized than C2-chlorine atom (+31% on V_{S,max}), which explains the involvement of the C2-bromine in Br•••π interactions in contrast to the C2-chlorine revealing no particular interaction. It is worth to note that the C2-Cl/Br atoms still have a significantly lower electrostatic potential than the N_D-Cl atom which is particularly well activated. The difference in activation of chlorine depending on its position is also clearly visible on its integrated topological atomic charge: whereas N_D-Cl is positively charged (+0.14 in (5,6-Cl)2•CH₃; +0.16 in 2•Cl), chlorine at positions C2 and C5,6 are negatively charged (−0.14 in 2•Cl; −0.21 in (5,6-Cl)2•CH₃).

Such strong chlorine activation at N_D position is indeed due to the amphoteric character of the imidazole ring. Calculations performed on two model compounds, where N_A in 2•Cl is replaced by either the CH- or CH₂-group, show a significant decrease of the V_{S,max} value at Cl at N_D position along the series (+29,42, +25,51 and +16,99 kcal/mol for N, CH and CH₂ groups, respectively). Furthermore, in addition to the amphoteric intramolecular effect, the intermolecular cooperativity effect in single chains assembled by N_D-Cl•••N_A interactions appears to be also significant. Increasing the *n* number of molecules in the chain affords a monotonic increase in the V_{S,max} value, ranging from +29,22 (*n* = 1) to +38.15 kcal/mol (*n* = 6) (Table S3). In contrast, such N_D-X•••N_A (X=Cl, Br, I) interactions were shown to exhibit an additive effect on a self-assembly of XB dimers and trimers.²⁶ Lastly, to check the effect of interchain π•••π interactions, we compared two anti-parallel chains assembled by N_D-Cl•••N_A and π•••π interactions (formed around inversion centres in the crystal structure). Consequently, this interaction induces the decrease of V_{S,max} values (for instance, from +29.22 to +27.84 kcal/mol for *n* = 1) while maintaining the cooperative effect with the increase of chain length (from +27.84 (*n* = 1) to +32.94 kcal/mol (*n* = 5)) (Table S4).

In conclusion, we have presented here synthesis and single-crystal structures of a new class of neutral self-complementary XB systems based on N-chlorobenzimidazole. In this series, strong activation of a sigma-hole on rather less polarizable Cl-atom primarily drives the molecular assemblies into halogen bonded 1D chains through short and directional Cl•••N contacts. With this respect, it should be pointed the synergetic intramolecular effects of electron withdrawing groups and the amphoteric character of the molecule, to which is added the intermolecular effect of cooperativity. Moreover, with the excellent self-association ability, this system also offers a vast structural diversity that allows introducing different substituents to tune the communication between the chains. These results open perspectives towards supramolecular synthesis of halogen bonded solid-state structures with a macroscopic polar arrangement.

This research was supported by the French National Research Agency Grant ANR-17-CE07-0025. A. D, O. J., M. F, and I.-J. thank the

CDIFX in Rennes for the use of X-ray diffractometer. The EXPLOR mesocenter is thanked for providing access to their computing facility (project 2021CPMXX2483).

Conflicts of interest

There are no conflicts to declare

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