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Using Halogen···Halogen Interactions to Direct Noncentrosymmetric Crystal Packing in Dipolar Organic Molecules

Binoy K. Saha,[†] Ashwini Nangia,*,[†] and Jean-François Nicoud[‡]

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India, and Groupe des Matériaux Organiques, Institut de Physique et Chimie des Matériaux de Strasbourg, CNRS et Université Louis Pasteur (UMR 7504), Strasbourg Cedex 2, France

ABSTRACT: Halogen atoms Cl, Br, and I steer crystallization of 2-halo-3-hydroxypyridine **1**, pyridine-*N*-oxides **2**, and 2-halo-3-aminopyridine **3** in noncentrosymmetric space groups efficient for nonlinear optical materials. Whereas the strong hydrogen-bond chains are aligned antiparallel, the L- or V-geometry of weak interhalogen interaction steers polar alignment in the solid state, even for high dipole moment (μ) halogenated *N*-oxides **2** ($\mu > 5.0$ D). Six out of seven structures evaluated crystallize in polar/chiral space groups due to interhalogen interactions compared to the one in six probability of noncentrosymmetric packing for achiral molecules.

Crystallization of achiral or racemic molecules in space groups that lack the inversion center continues to be a challenge since the early days of crystal engineering.[1] Crystal structures with noncentrosymmetric packing of molecules are important as electrooptic and nonlinear optical materials;[2] enantiomorphous crystals are useful in asymmetric synthesis and provide insight into the evolution of chirality in nature. Centrosymmetric packing is favored for typical organic molecules having hydrogen-bonding functional groups and hydrophobic alkyl/aryl substituents because of the antiparallel alignment of dipoles (charge cancellation in neighboring domains) and the universality of close packing in molecular crystals (bumps fit into hollows). Only 10−15% of achiral organic molecules crystallize in noncentrosymmetric space groups, such as $P2_1$, $P2_12_12_1$, $Pca2_1$, $Pna2_1$, $Fdd2$, Cc, etc.[3] Meta-substituted nitrobenzenes have a higher probability for polar/chiral crystallization (40%) because of their dissymmetric shape.[4] Among the various approaches being tried to produce nonlinear optical (NLO) crystals, e.g., vanishing dipole moment (μ) (POM),[1b] octupolar molecules,[5] and diamondoid networks,[6] the only guaranteed solution to avoiding the inversion center is to use chiral molecules (e.g., NPP).[1b] A better understanding of the factors that promote polar organization of achiral molecules in the solid state is important for crystal engineering and supramolecular materials.

Our approach to promote noncentrosymmetric crystallization of dipolar molecules is summarized in Scheme 1. The strong hydrogen-bonding functional groups will usually align antiparallel (big outline arrows). If a halogen atom is placed in the molecule, roughly orthogonal to the main dipole vector (small shaded arrows), then the overall structure would be noncentrosymmetric because of the L- or V-shaped geometry in X···X interactions;[7] L-geometry typically occurs across 2_1 screw-axis or glide plane, whereas V-geometry is possible about 2-fold rotation symmetry.

To test our hypothesis, 2-halo-3-hydroxypyridine **1** (X = Cl, Br, I) compounds were synthesized from the parent compound. Crystals of **1Cl**, **1Br** and **1I** were grown from EtOAc.[8] Chains of O−H···N hydrogen bonds run in opposite directions in **1H**,[9] a typical packing motif in the centrosymmetric $P2_1/c$ space group. In contrast, **1Cl** crystallizes in the polar space group $Fdd2$, and **1Br** and **1I** have isostructural packing in the $Pna2_1$ space group. These space groups are devoid of the inversion center, a necessary condition for SHG activity of optical crystals. Antiparallel chains of O−H···N hydrogen bonds (2.12 Å, 130.1°) between glide related molecules run along the a-axis in **1I**. The polar arrangement arises due to short I···I interaction of L-geometry (3.74 Å, C−I···I 174.4°,

Scheme 1. (a) Interhalogen Interaction Types. (b) Noncentrosymmetric Alignment of Hydrogen-Bond Chains Due to L- or V-geometry of X···X Interactions. (c) 3-Pyridinol 1, Pyridine-*N*-Oxide 2, and 3-Aminopyridine 3 Structures
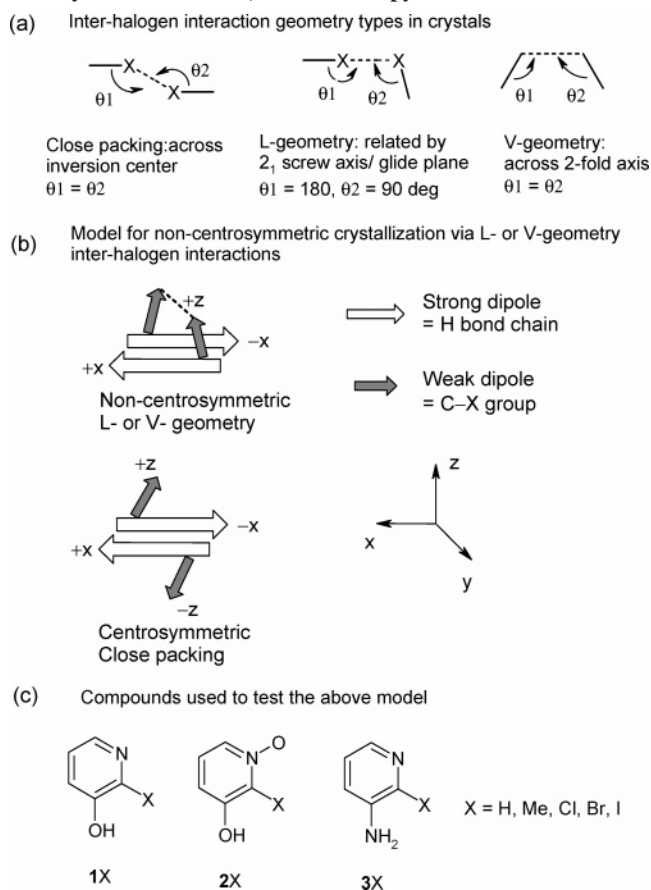

114.5°) between the polarizable iodine atoms (Bondi's van der Waals radius: Cl 1.75 Å, Br 1.85 Å, I 1.98 Å). C−I vectors of molecules in (021) and (02$\bar{1}$) planes generate a net dipole along the $−c$ direction (Figure 1). **1Br** has an identical polar arrangement of hydrogen-bonded molecules (2.06 Å, 150.9°) directed by short Br···Br interaction (3.64 Å, C−Br···Br 170. 2°, 121.2°). Cl atoms related by 2-fold axis[10] (3.35 Å, 158.9°, 158.9°) connect hydrogen-bond chains in **1Cl** (O−H···N: 1.92 Å, 164.9°; Figure 2). Noting the isostructurality of **1Br** and **1I**, we attempted synthesis of the ethynyl analogue[11] but instead isolated the cyclized benzofuran (see Supporting Information). The parallel alignment of molecules in halogenated **1** compared to the centrosymmetric structure of **1Me**
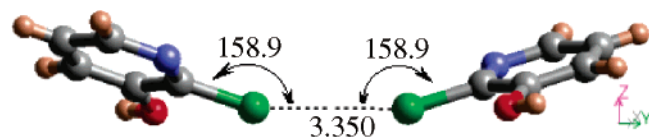
* To whom correspondence should be addressed. E-mail: ashwini_nangia@rediffmail.com. Fax: +91 40 23011338.
† University of Hyderabad.
‡ CNRS et Université Louis Pasteur (UMR 7504).e
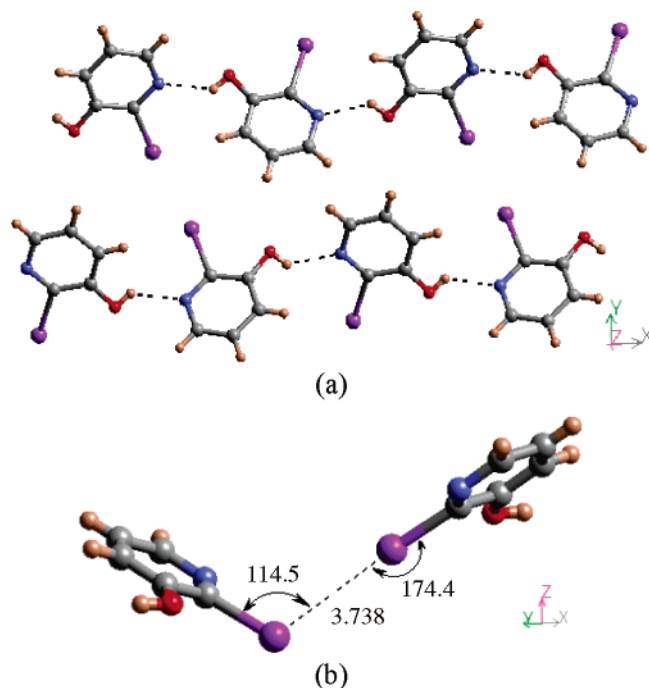
Figure 1. (a) Antiparallel chains of O−H⋯N hydrogen bonds in **1**I. (b) Polar alignment of molecules due to the L-geometry of I⋯I interactions between adjacent chains. **1** Br is isostructural.


Figure 2. V-geometry of Cl⋯Cl interaction across a 2-fold rotation axis in **1**Cl.

(*C*2/*c*) highlights the polarity-inducing ability of interhalogen interactions in hydrogen-bonded crystal structures (Figure 3). A view down the hydrogen-bond chain axis shows that the angle at which the molecular planes intersect is different in Cl, Br, and I derivatives. If the intersection of aromatic rings is viewed as an X junction (Figure 4), halogen⋯halogen interactions serve as the supramolecular handle to modify the hinge angle, θ_{ip}, which in turn increases the NLO response of the iodo derivative (Table 1).

A situation similar to Scheme 1b will also prevail in 2-halo-3-hydroxypyridine-*N*-oxide **2** and 2-halo-3-aminopyridine **3**.[8] Crystals of **2**Br from MeOH (Figure 5, space group $P2_12_12_1$) contain O−H⋯O⁻ chains (1.88 Å, 175.7°) along [001] and [00$\bar{1}$]. Bromine atoms of antiparallel chains engage in the L-shaped interaction (3.93 Å, 171.5°, 126.1°). Similarly, the chloro derivative **2**Cl is weakly SHG active (Cl⋯Cl 3.51 Å, *Pna*2₁ space group). Continuing further, **3**Br crystalizes (from CHCl₃) in the enantiomorphous $P2_1$ space group via N−H⋯N H bonds and L-shaped Br⋯Br interactions (3.64 Å, 177.8°, 102.6°) between symmetry-independent molecules ($Z' = 4$); the second Br⋯Br contact (3.63 Å, 148.1°, 102.5°) has borderline L/V-geometry (Table S1, Supporting Information). However, **3**Cl is centrosymmetric ($P2_1/n$,) and devoid of Cl⋯Cl interactions; its packing is similar to **2**Me in the $P2_1/c$ space group.

There are several factors that permit us to implicate specific, structure-directing X⋯X interactions. (1) The interplay of hydrogen bonding and interhalogen interactions shows greater emphasis on hydrogen bonding in chloro, whereas X bonding becomes significant in bromo/iodo structures, consistent with the better polarizability of heavier halogens.[7,12] Accordingly, the interaction geometry is more L-shaped for iodo than bromo, whereas chloro has V-shaped interaction (Scheme 1a). (2) Iodo compound **1**I shows the highest optical response, thanks to optimal polar alignment of dipoles in
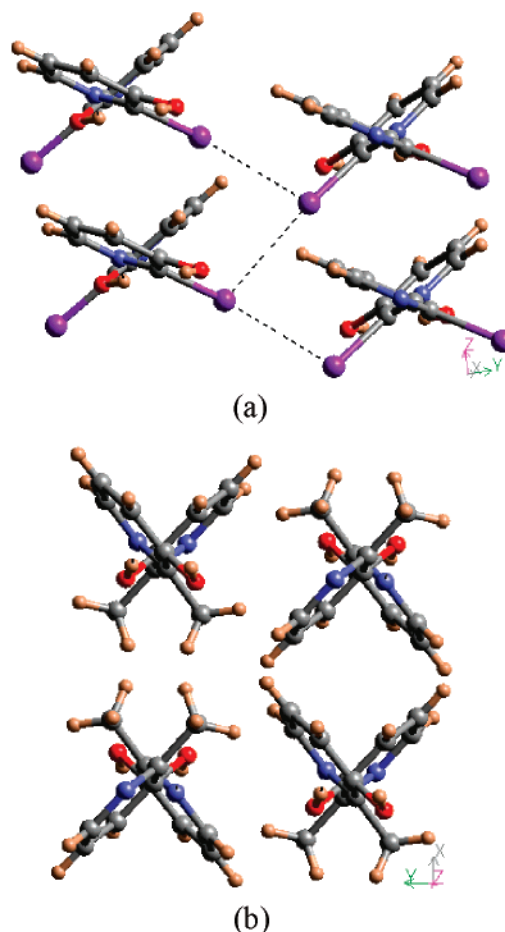
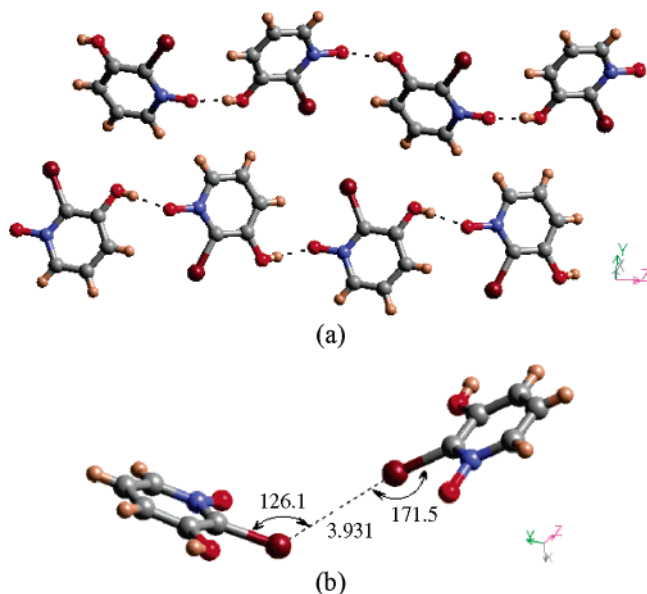**Figure 3.** Noncentrosymmetric crystalline solid **1**I (a) and centrosymmetric structure **1**Me (b).
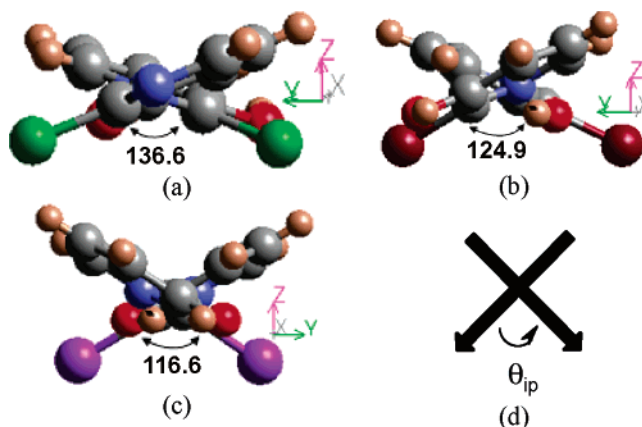
Figure 4. Halogen⋯halogen interactions modulate the (d) interplanar hinge angle (θ_{ip}) between O−H⋯N hydrogen-bonded chains in **1**Cl, **1**Br, and **1**I (a−c).

its crystal (Figure 4). SHG values in Table 1 bear out these molecular and crystal structure trends. (3) Methyl derivatives **1**Me and **2**Me are centrosymmetric, whereas halogenated compounds are noncentrosymmetric and SHG active. When methyl and halogen crystal structures are different, specific interhalogen interactions are usually involved.[13] The most significant observation is that the halogen derivatives adopt noncentrosymmetric packing even though their dipole moment is higher than that of H/Me compounds. On the basis of a recent statistical analysis of diphenyl ethers,[14] molecules with a $\mu < 4$ have a 7:3 preference for centrosymmetry, whereas molecules with $\mu > 4$ almost always adopt centrosymmetric packing (AM1 values). We show that optimized interhalogen

compound	space group[c]	SHG activity	μ (Debye)
1Cl	*Fdd*2 (*)	<urea	3.88
1Br	*Pna*2₁ (*)	<urea	3.94
1I	*Pna*2₁ (*)	≈urea	3.88
1Me	*C*2/*c*	nil	2.62
2Cl	*Pna*2₁ (*)	<urea	5.28
2Br	*P*2₁2₁2₁ (*)	very weak	5.23
2Me	*P*2₁/*c*	nil	4.54
2H	*P*1̄	nil	4.88
3Cl	*P*2₁/*n*	nil	3.49
3Br	*P*2₁ (*)	<urea	3.61

[a] μ, calculated in AM1. [b] Measured using Nd^{3+}-YAG laser at 1064 nm. [c] Note the high frequency of noncentrosymmetric space groups (*).

(a)

(b)

Figure 5. (a) Antiparallel chains of O−H···O⁻ hydrogen bonds in **2**Br. (b) Note the L-shaped Br···Br interaction and the similarity with Figure 1.

interactions can induce noncentrosymmetric crystallization even in highly dipolar molecules, like halogenated pyridine-*N*-oxides **2** (μ > 5, Table 1). Notwithstanding that the absolute NLO activity is modest (≤ urea), because there is no extended push−pull conjugation in the molecule, we emphasize that the role of halogen atoms Br and I, and to a lesser extent Cl, as steering groups for noncentrosymmetric crystallization is unprecedented.[15] CN···X synthon (X = Br, I) and steric factors (*i*-Pr instead of Me) have been exploited in recent papers[16] to favor polar alignment of one-dimensional (1D) dipoles. An advantage with pyridinols **1/2** and pyridylamine **3** as potential organic NLOs is that they are transparent above 350 nm.

A noncentrosymmetric space group is the first of many conditions for NLO materials because other factors such as phase-matching, transparency/efficiency tradeoff, and thermal stability also must be optimized.[2] The best space groups for NLO crystals is *P*2₁ followed by *Pca*2₁, *Pna*2₁, *Fdd*2, whereas the most populated enantiomorphous space group *P*2₁2₁2₁ is less efficient.[17] Exploiting halogen···halogen interactions for steering polar crystallization favors the more efficient NLO space groups because of Coulombic attraction[7,12] and appropriate symmetry operators in the L/V-geometry (Scheme 1a). The major difficulty in molecular and crystal engineering of NLO solids is that increasing molecular hyperpolarizability (β) in NLO-phores through push−pull conjugation also favors centrosymmetric alignment of the strong dipoles. We report a strategy that generates polar crystalline order in 6/7 halogenated structures even as the strong hydrogen-bond chains run antiparallel across three families of structures in 10 molecules.

The predominant trend of dipolar molecules for centrosymmetry is reversed toward functional NLO solids by molecular and crystal engineering. With halogenated derivatives of **1**, **2**, and **3** showing SHG activity, we plan to install biphenyl and styryl groups at C2 with pendant halogen atoms to steer polar alignment of molecular chromophores. This approach is easily implemented in other meta-substituted benzenes such as *m*-nitrophenol and *m*-nitroaniline. We believe that our model will best apply when the C−X dipole is roughly orthogonal to the strong hydrogen-bond chain; otherwise, centrosymmetric packing will dominate over the weak halogen··· halogen effect. Remarkably, the frequency for noncentrosymmetric crystallization in our achiral test compounds is significantly higher than the statistical 1 in 5 chance of obtaining chiral/polar crystals.

Supporting Information Available: Synthesis of **1** and **2**, scatter plot of X···X contacts and interaction geometry, powder XRD plots, and crystallographic data for **1**−**3** derivatives (.cif) are available free of charge via the Internet at http://pubs.acs.org.

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(8) Synthesis of compounds **1**−**3** is given in Supporting Information. Crystal data were collected on Bruker SMART APEX CCD with Mo Kα radiation (λ = 0.71073 Å). 2-Chloro-3-hydroxypyridine (**1**Cl): C_5H_4ClNO, M_r = 129.54, orthorhombic, *Fdd*2, *a* = 23.069-(4), *b* = 25.231(4), *c* = 3.8429(6) Å, *V* = 2236.8(6) Å³, *Z* = 16, *R*1 = 0.0295, *wR*2 = 0.0764, *T* = 298 K. 2-Bromo-3-hydroxypyridine (**1**Br): C_5H_4BrNO, M_r = 174.00, orthorhombic, *Pna*2₁, *a* = 11.5563-(12), *b* = 12.7285(13), *c* = 3.8875(4) Å, *V* = 571.83(10) Å³, *Z* = 4, *R*1 = 0.0198, *wR*2 = 0.0507, *T* = 100 K. 2-Iodo-3-hydroxypyridine (**1**I): C_5H_4INO, M_r = 220.99, orthorhombic, *Pna*2₁, *a* = 11.5329-(11), *b* = 12.8331(12), *c* = 4.2475(4) Å, *V* = 628.64(10) Å³, *Z* = 4, *R*1 = 0.0172, *wR*2 = 0.0457, *T* = 100 K. 2-Methyl-3-hydroxypyridine (**1**Me): C_6H_7NO, M_r = 109.13, monoclinic, *C*2/*c*, *a* = 11.053-(2), *b* = 9.6151(19), *c* = 11.316(2) Å, β = 100.64(3)°, *V* = 1181.9(4) Å³, *Z* = 8, *R*1 = 0.1495, *wR*2= 0.3050, *T* = 100 K. 2-Chloro-3-hydroxypyridine-*N*-oxide (**2**Cl): $C_5H_4ClNO_2$, M_r = 145.54, ortho-rhombic, *Pna*2₁, *a* = 11.2712(14), *b* = 12.7754(16), *c* = 3.7794(5) Å, *V* = 544.21(12) Å³, *Z* = 4, *R*1 = 0.0266, *wR*2 = 0.0617, *T* = 100 K. 2-Bromo-3-hydroxypyridine-*N*-oxide (**2**Br): $C_5H_4BrNO_2$, M_r = 190.00, orthorhombic, *P*2₁2₁2₁, *a* = 3.8571(5), *b* = 12.3235(15), *c* = 12.5884(15) Å, *V* = 598.36(13) Å³, *Z* = 4, *R*1 = 0.0252, *wR*2 = 0.0589, *T* = 298 K. 2-Methyl-3-hydroxypyridine-*N*-oxide (**2**Me): $C_6H_7NO_2$, M_r = 125.13, monoclinic, *P*2₁/*c*, *a* = 4.6258(9), *b* = 10.3353(19), *c* = 12.677(2) Å, β = 99.270(3)°, *V* = 598.18(19) Å³, *Z* = 4, *R*1 = 0.0487, *wR*2 = 0.1346, *T* = 298 K. 3-Hydroxypyridine-*N*-oxide (**2**H): $C_5H_5NO_2$, M_r = 111.10, triclinic, *P*-1, *a* = 6.3536-(8), *b* = 6.5014(8), *c* = 6.9499(8)Å, α = 113.794(2), β = 99.650(2), γ = 106.930(2)°, *V* = 237.59(5) Å³, *Z* = 2, *R*1 = 0.0398, *wR*2 = 0.1055, *T* = 298 K. C2 is disordered over two positions (C2A, C2B) with 0.5 occupancy. Similarly N1 and OH hydrogen are disordered

over two positions (N1A, N1B and H1, H2) with 0.5 occupancy. 2-Chloro-3-aminopyridine (3Cl): $C_5H_5ClN_2$, M_r = 128.56, monoclinic, $P2_1/n$, a = 6.446(5), b = 8.022(6), c = 11.991(8)Å, β = 104.510(11)°, V = 600.3(7) Å^3, Z = 4, $R1$ = 0.0429, $wR2$ = 0.1222, T = 298 K. 2-Bromo-3-aminopyridine (3Br): $C_5H_5BrN_2$, M_r = 173.02, monoclinic, $P2_1$, a = 7.9689(5), b = 13.1908(8), c = 11.6096(7) Å, β = 104.6860(10)°, V = 1180.49(13) Å^3, Z = 8, $R1$ = 0.0243, $wR2$ = 0.0588, T = 100 K. For all structures, intensities were corrected for absorption effects using the multiscan technique SADABS. All non-hydrogen atoms were refined anisotropically. H atoms connected to C were generated by riding model, and H atoms connected to oxygen were located in difference electron density maps. Structure solution and refinement were carried out with Bruker SHELXTL.

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