▐ **Organic & Supramolecular Chemistry**

Interplay of Hydrogen and Halogen Bonding in the Crystal Structures of 2,6-Dihalogenated Phenols

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Hydrogen and halogen bonds are important anisotropic attractive interactions in the molecular crystalline state. 2,6-dibromophenol (**1**) was analyzed by single-crystal X-ray diffraction for the first time. The intermolecular interaction pattern was studied by Hirshfeld surface analysis along with 2D fingerprint diagrams. The characteristic interactions that dominate the crystal packing are electrostatic type-II Br···Br interactions, O—H···O hydrogen bonds, and an offset parallel π-stacking arrangement. Compound **1** was compared with 2,6-difluoro- (**2**) and 2-bromo-6-chlorophenol (**3**) in terms of their interplay between hydrogen and halogen bonding. Whereas the O—H···O hydrogen bond is more pronounced in the lighter homologues, the halogen···halogen interaction becomes a particularly important directional, attractive interaction in the crystal structure of 2,6-dibromophenol.

Introduction

Halogenated aromatic rings[1,2] and phenols[3,4] are common structural motifs in natural products and often form an integral part in compound collections inspired by them,[5] many of which have remarkable biological activity. Both classes of compounds represent key intermediates in organic synthesis.[6–9] Aryl halides are of particular importance as electrophiles in C—C coupling reactions,[10–13] which makes the development of new, efficient synthetic strategies a worthwhile task.[14–19] In recent years, efforts have been made to develop new synthetic routes particularly to halogenated phenols,[20–24] which have also been used as antibacterial agents.[25]

Halogen bonds have been studied for a long time and are still a research topic of highest interest.[26–29] The number of contributions in this field during the past few years is significant and covers a wide area, from understanding the

nature of this kind of noncovalent interactions[30–38] to the targeted design of halogene-based supramolecular entities[39–44] and applications in organocatalysis.[45,46] Studies on halogenated molecules interacting with biomolecular systems have opened up entirely new approaches in drug development.[47–50] Mixed halogenated benzene derivatives and their co-crystallization behavior have attracted increased attention in view of their intermolecular interactions.[51–53]

During our work with 2,6-dibromophenol (**1**) as a starting material for functionalization reactions on the aryl ring, we found, to our surprise, that the crystal structure has not yet been investigated, and that the structure of the 2,6-difluoro analogue (**2**) has only recently been elucidated crystallographically.[54] A literature search revealed that crystallographic data are also available for one-component single-crystalline 2,6-dichloro-[55] and 2-bromo-6-chlorophenol (**3**).[56] 2,6-Difluorophenol exhibits excellent hydrogen bonding abilities[57] and 2,6-dichlorophenol is found in a few co-crystals.[58–60] The crystal structure of pure 2,6-diiodophenol, although it builds an important subunit of the thyroid hormone 3,5,3′,5′-tetraiodo-L-thyronine (T$_4$),[61] is still unknown. However, it has been structurally characterized as a guest molecule enclosed in a macrocyclic metallohost through iodine···aryl and π···π interactions.[62] It is known that 2,6-substituted phenols have interesting biological activity, as the example of propofol (i.e. 2,6-diisopropylphenol) shows, a widely used intravenous general anaesthetic.[63] Given the importance of 2,6-dihalophenols in understanding halogen bonding principles in nature and in artificial supramolecular architectures, and driven by our interest in noncovalent interactions in molecular crystals,[64–69] it seemed all the more important to investigate the heavier 2,6-dibromophenol (**1**) more closely with respect to its intermolecular interaction pattern in the crystalline state.

Herein, we report for the first time on the crystal structure of 2,6-dibromophenol (**1**) and perform a model study focusing on the intermolecular interactions in crystal packings of 2,6-dihalophenols, especially with regard to hydrogen and halogen bonds. The noncovalent interactions within molecular crystals of the heavy 2,6-dibromophenol are compared with those of the two lighter homologues **2**[54] and **3**[56] with the aim of identifying basic structural principles. For our analysis we used Hirshfeld surfaces[70] along with two-dimensional (2D) fingerprint plots,[71] and quantum chemical calculations.
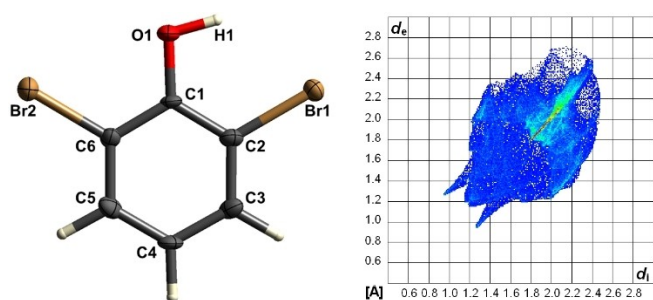
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Results and Discussion

2,6-Dibromophenol (**1**) crystallized from hexane at −30 °C in the orthorhombic crystal system, space group $P2_12_12_1$ (Figure 1 and Table 1), which is the same as for all other known crystal structures of 2,6-dihalophenols.[54–56] The Br−C bond lengths with 1.883(7) Å and 1.893(7) Å differ only slightly. The molecule is absolutely flat, with the O−H bond pointing to the Br1 atom (H1···Br1 2.518 Å), which might be due to the large polarizable bromine atom in the *ortho* position.[35] The C1−O1−H1 angle is noticeably reduced to 103.15°. Figure 1, right, shows the 2D fingerprint diagram of 2,6-dibromophenol (**1**). Three main structural pattern can be identified, which are characteristic for the description of the intermolecular interactions. There are 1) the distinct spikes, i.e. the point on the Hirshfeld surface where

$d_i \approx 1.3$ Å and $d_e \approx 1.0$ Å, 2) the blue-green area around $d_i = d_e \approx 1.8$ Å, which is traversed by 3) a dark red stripe.

The spikes are typical for hydrogen bonds and belong to intermolecular O−H···O contacts between the hydroxyl groups (actually found in the crystal structure: H1···O1 2.314 Å, O1···O1 2.813 Å) (Figure 2). Although the distances are below the sum of the van der Waals radii,[72,73] this hydrogen bond is more likely located on the weaker end of the strength scale according to *Jeffrey's* classification,[74] with a more electrostatic rather than covalent contribution.[75] The reasons may be attributed to the competition between intra- and intermolecular hydrogen bonding, which is also reflected by the small O−H···O angle of 123.27° for the intermolecular hydrogen bond. The influence of the fluorine substitution on the O−H···O hydrogen bond is considerable[54] and causes sharp spikes in the 2D fingerprint plot, which are more pronounced here than in compound **1** (Figure 3, left). In the crystal structure of 2,6-difluorophenol (**2**), the O−H bond is slightly turned out of the ring plane by approximately 25°. The bond parameters of the O−H···O hydrogen bond in compound **2** (O−H 0.814 Å, H···O 2.002 Å, O···O 2.805 Å, O−H···O 168.77°) show a significant shortening of the H···O contact together with a strong expansion of the O−H···O angle in the direction of linearity, and are thus in a range that is also found in O−H···O hydrogen bonds of halogenated aliphatic alcohols.[76] One explanation for the stronger O−H···O hydrogen bonding in **2** may be the increased acidity of the hydroxyl group due to fluorine substitution.[35,77] This effect is supported by our DFT calculations on the M062X/6-311+G(d,p) level of theory, which gave
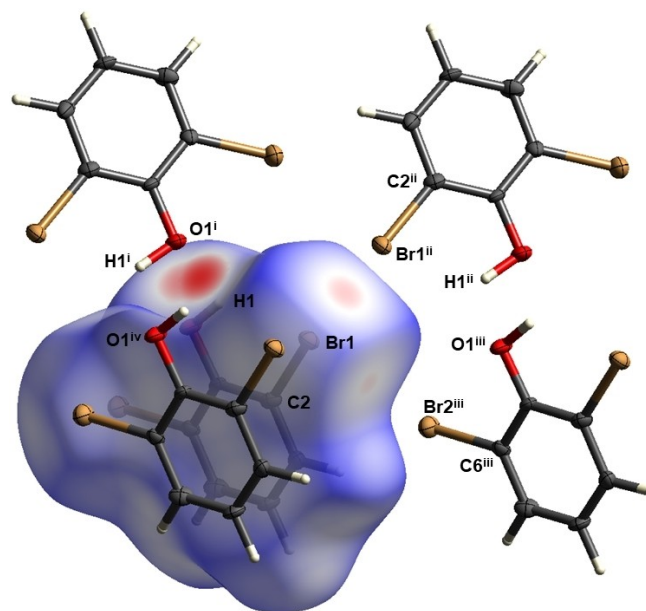

Figure 1. Molecular structure (displacement ellipsoids set at the 50% probability level) and 2D fingerprint plot (showing all contributions of intermolecular contacts) of 2,6-dibromophenol (**1**) in the crystal. Selected bond lengths [Å]: C1−O1 1.361(8), Br1−C2 1.883(7), Br2−C6 1.893(7). Intramolecular hydrogen bond: O1−H1 0.773 Å, H1···Br1 2.518 Å, C1−O1−H1 103.15°, O1−H1···Br1 132.44°.

Table 1. Crystal data and structure refinement of 2,6-dibromophenol (**1**).

Empirical formula	$C_6H_4Br_2O$
Formula weight [g mol^{-1}]	251.91
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a [Å]	4.14160(10)
b [Å]	7.5396(2)
c [Å]	22.2479(5)
Volume [Å^3]	694.71(3)
Z	4
Density (calculated) ρ [g cm^{-3}]	2.409
Absorption coefficient μ [mm^{-1}]	14.075
$F(000)$	472
Crystal size [mm^3]	0.14×0.03×0.02
Theta range for data collection θ [°]	3.974–66.684
Index ranges	$-3 \leq h \leq 4$
	$-8 \leq k \leq 8$
	$-26 \leq l \leq 26$
Reflections collected	6083
Independent reflections	1222 ($R_{int} = 0.0586$)
Completeness to $\theta = 66.684°$	99.9%
Data/restraints/parameters	1222/0/98
Goodness-of-fit on F^2	1.058
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0326$, $wR2 = 0.0832$
R indices (all data)	$R1 = 0.0340$, $wR2 = 0.0853$
Largest diff. peak and hole [e Å^{-3}]	0.718 and −0.758

Figure 2. Hirshfeld surface of 2,6-dibromophenol (**1**) highlighting the O−H···O hydrogen bonds, the Br···Br interactions, and the offset parallel π-stacking in the crystal packing. Selected distances [Å] and angles [°]: H1···O1 2.314, O1···O1 2.813, O1−H1···O1 123.27, C2−Br1···Br1−C2 3.568 ($\theta_1 = 170.97°$, $\theta_2 = 116.13°$), C2−Br1···Br2−C6 3.647 ($\theta_1 = 163.56°$, $\theta_2 = 104.08°$). Symmetry transformations used to generate equivalent atoms: (i) −0.5 + x, 0.5 − y, 1 − z; (ii) −0.5 + x, 1.5 − y, 1 − z; (iii) −1 + x, 1 + y, z; (iv) −1 + x, y, z.

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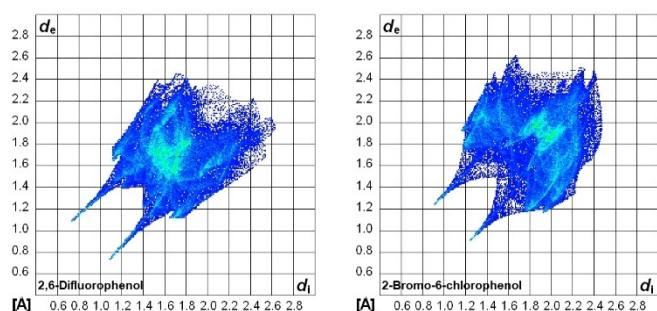
Figure 3. 2D fingerprint plots (showing all contributions of intermolecular contacts) of 2,6-difluorophenol (**2**)[54] and 2-bromo-6-chlorophenol (**3**).[56]

insight into the mobility of the hydroxyl hydrogen atom in 2,6-dihalogenated phenols (for details, see the Supporting Information). The activation barrier for the exchange between the two intramolecular O—H···Hal hydrogen bonds was found to be 4.3 kcal mol^{-1} (**1-TS$^+$**) for the dibromo compound **1** and 3.3 kcal mol^{-1} (**2-TS$^+$**) for the difluoro derivative **2**. This can be regarded as an indirect measure of the ability of the hydroxyl group to participate in hydrogen bonding and proves a higher flexibility of the O—H bond in compound **2**.

What is most striking about compound **1** is the dark red stripe in the fingerprint plot with the closest contacts at $d_i = d_e \approx 1.8$ Å, which roughly corresponds to the van der Waals radius of bromine[72,73] and can be assigned to Br···Br interactions (18.2%) (Figure 1). The closest distances that can be found are 3.568 Å (Br1···Br1) and 3.647 Å (Br1···Br2) (Figure 2). Halogen bonds have both a directional electrostatic and a dispersion component.[35] A more detailed analysis of the halogen···halogen interaction pattern in compound **1** shows that they can be classified as electrostatically-driven highly directional type-II C—Br···Br—C interactions.[27,32,53,78] θ_1 and θ_2, i.e. the two C—Hal···Hal angles, are diagnostic for the nature of the halogen bond and ideally have values of $\theta_1 \approx 180°$ and $\theta_2 \approx 90°$ in σ-hole type-II C—Hal···Hal—C interactions.[27,32,78] The σ-hole is the result of an anisotropic charge density distribution around the C—Hal bond leading to a positive electrostatic potential at the outermost region along the extension of the C—Hal bond (charge depletion) and concomitantly to an equatorial belt of negative electrostatic potential (charge concentration) around the halogen atom.[31–35] The θ_1 (170.97° and 163.56°) and θ_2 (116.13° and 104.08°) angles in our simplyfied halogenated model system **1** nicely reflect this kind of highly directional and attractive interaction mode (Figure 2). The comparison with the lighter homologues **2** and **3** clearly shows how this type of interaction is becoming less directional and less important with incrasing electronegativity of the halogen substituents (clearly recognizable by the lack of strong Hal···Hal interactions in the fingerprint diagrams, Figure 3), while the O—H···O hydrogen bond becomes all the more important in the same direction (visible at the sharp spikes, Figure 3). The geometrical parameters (θ_1 and θ_2) of the two shortest F···F contacts in 2,6-difluorophenol (**2**) are $\theta_1 = 76.65°$ and $\theta_2 = 77.93°$ (F···F 3.217 Å) and $\theta_1 = 105.77°$ and $\theta_2 = 110.88°$ (F···F 4.246 Å).[54] This indi-

cates that the F···F contacts in **2** (2.8%) are more of a dispersion-like nature, since the θ angles meet the conditions for type-I C—Hal···Hal—C interactions ($\theta_1 \approx \theta_2$) quite well.[27,32,53,78] In 2-bromo-6-chlorophenol (**3**), the dihalogen contacts are exclusively unsymmetrical type-I Br···Cl interactions (3.2%), although a σ-hole-type[53] C—Br···π contact (Br···C 3.362 Å, C—Br···C 177.06°) can also be found.[56] The molecular electrostatic potentials (ESPs) of compounds **1–3** within the crystal packings[79] give a nice impression of the anisotropic charge distribution around the C—Br bonds and of the isotropic negative electrostatic potential around the C—F bonds (see the Supporting Information).

A characteristic packing feature of all three halogenated phenols is the offset parallel π-stacking arrangement, which is least pronounced in the 2,6-difluoro compound. The blue-green area in the 2D fingerprint plot of 2,6-dibromophenol (**1**) centered around $d_i = d_e \approx 1.8$ Å (Figure 1) is close to the van der Waals radius of carbon[72,73] and represents the π···π interactions in the stacking arrangement.[71] Our investigation of interplaying intermolecular interactions in halogenated phenols may contribute to a better understanding of the tunability of noncovalent interactions.[80]

Conclusions

In conclusion, a model study on the interplay of hydrogen bonding and halogen···halogen interactions in molecular crystals was performed. 2,6-Dibromophenol (**1**), which was structurally characterized for the first time, was compared with 2,6-difluoro- (**2**) and 2-bromo-6-chlorophenol (**3**). The crystallographically uniform space group for all 1,2-dihalophenols allows for a well-balanced interplay between hydrogen and halogen bonds. Of all examined compounds, Hal···Hal interactions have the greatest directional importance in the dibromo derivative **1**. Interestingly, the O—H···O hydrogen bond plays a subordinate role compared to compounds **2** and **3**, with the hydroxyl hydrogen atom additionally participating in an intramolecular O—H···Br hydrogen bond in **1**. In compounds **2** and **3**, the Hal···Hal interactions are of the dispersion-dominated type-I and much less pronounced than in **1**. Offset parallel π-stacking plays a role in all three compounds. However, the displacement of the parallel layers increases in the direction of 2,6-dibromo-, via 2-bromo-6-chloro-, to 2,6-difluorophenol. We assume that our thorough investigation into the hydrogen and halogen bond interaction pattern of 2,6-dihalogenated phenols, which can be considered as basic molecular building blocks for targeted supramolecular assemblies, are of general importance for fine-tuning structure-forming noncovalent interactions that are useful for various application tasks, as outlined in the introductory section.

Deposition Number 2083061 (for **1**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Supporting Information Summary

Spectroscopic data of compound **1**, details on X-ray crystallography including the crystal packing of compound **1**, molecular electrostatic potentials (ESPs) of compounds **1**–**3**, and details on quantum chemical calculations can be found in the Supporting Information.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Keywords: halogenated phenols · halogen···halogen interactions · hydrogen bonds · molecular crystals · self-assembly

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