

Halogen Bonding and Isostructurality in 2,4,6-Tris(2-halophenoxy)-1,3,5-triazines

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ABSTRACT: Crystal structures of 2,4,6-tris(2-halophenoxy)-1,3,5-triazines (halo = fluoro, chloro, bromo, iodo; 2-XPOT) are discussed in the background of 3-halophenoxy (3-XPOT) and 4-halophenoxy (4-XPOT) structures. Among inter-halogen interactions, the electrostatic L-shaped type II interactions are generally shorter than the inversion-related type I geometry in 2-halo compounds. π -Stacking of triazine rings at van der Waals separation (~ 3.5 Å) makes the well-known Piedfort Unit assembly and the halogen atoms form a trimer motif. 2-FPOT and 2-ClPOT are 2D isostructural but there are differences in the complete 3D molecular packing. 2-BrPOT and 2-IPOT are a 3D isostructural pair and their isomorphous unit cells have a similarity index of 0.008. The position of the halogen atom causes structural differences in 2-, 3-, and 4-XPOT compounds, with the para-series showing guest inclusion and the ortho- and meta-compounds having single-component close-packed structures. The Cambridge Structural Database is analyzed for structural mimicry upon halogen GRoup eXchange (GRX). Chloro-, bromo-, and iodo-substituted compounds of the same molecule (56 clusters) are isostructural in 30% cases, Cl/Br are identical in 66% pairs, and Br/I in 50% examples of the subdatabase. © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:185–194, 2007; Published on-

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INTRODUCTION

Halogens can make short contact with respect to their van der Waals radius sum. Cl₂, Br₂, and I₂ molecules participate in the side-on inter-halogen interaction in their orthorhombic crystal structures (Cmca) [1]. Sakurai et al. [2a] noted a directional preference in the Cl \cdots Cl contact in the crystal structure of 2,5-dichloroaniline.* There is considerable overlap between the spherical atoms but isotropic atom–atom potential is inadequate to explain several features showed by the halogen atoms. Bondi [3] first observed that the effective shapes of some atoms might not be truly spherical but rather ellipsoid or pear-shaped, especially for the heavier elements. Nyburg and Faerman [4] showed that the atomic radii of nonspherical halogen atoms along the C–X bond vector are shorter than the distance perpendicular to it. This so-called polar flattening in organic chlorine (and heavier halogens) has led to considerable speculation whether short directional contacts are due to attractive forces or because of a minimum in the repulsive potential. According to the prevailing model, halogen \cdots halogen contacts have two preferred geometries, type I ($\theta_1 \cong \theta_2$) and type II ($\theta_1 \cong 180^\circ$ and $\theta_2 \cong 90^\circ$), as shown in Fig. 1. Desiraju and Parthasarathy [5] emphasized specific attractive forces between halogens on the basis of the L-shaped geometry of X₂ in the gas phase as well as

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*This structure was redetermined to high accuracy by Cox [2b].

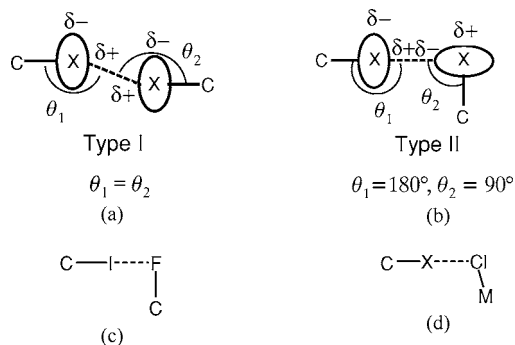


FIGURE 1 Inter-halogen interactions: (a) Type I and (b) type II geometry. Bent geometry in C—I...F—C and C—X...Cl—M interactions (c and d) consistent with the electrostatic stabilization shown in (b).

statistical analysis of halogenated hydrocarbon crystal structures by considering the halogen...halogen contact area with respect to the total molecular area. On the other hand, Price et al. [6] explained the directionality to anisotropic electrostatic forces and exchange repulsion without significant contribution from charge transfer, discarding the possibility of specific inter-chlorine contacts. Their computational

results suggest that Cl...Cl interactions are quite normal, with repulsion, dispersion, and electrostatic contributions being the most important, but that the nonsphericity of the chlorine charge distribution has a significant effect on these contributions [6–8].

The heavy halogens are polarized positively in the polar region (along the C—X vector) and negatively in the equatorial region (perpendicular to the C—X vector). The atomic size, radial anisotropy, and polarization increase in the order Cl < Br < I whereas electronegativity changes are in the reverse direction [9]. Thus, in the case of unsymmetrical inter-halogen interactions, e.g. C—F...I—C, the negative equatorial part of the lighter halogen preferentially approaches the positive polar region of the heavier halogen [10]. Anionic metal halides also show a strong directionality to interact with the polar region of the organic halogen [11]. Brammer and coworkers [12,13] showed that the role of inorganic halide (M—Cl) and organic halogen (C—X) are distinct and different in crystal packing. The C—X...Cl angle is linear (150–170°) whereas the M—Cl...X angle is markedly bent (120–130°) in

TABLE 1 Interaction Geometries in 2-XPOT Crystal Structures^a

Compound	Interaction	<i>d</i> (Å)	<i>D</i> (Å)	θ (°)
2-FPOT	C(9)—H...N(3)	2.60	3.560(2)	147.7
	C(14)—H...N(1)	2.74	3.527(3)	129.6
	C(17)—H...O(1)	2.75	3.604(3)	135.0
	C(18)—H...F(1)	2.39	3.310(4)	141.9
2-CIPOT	C(10)—H...N(2)	2.66	3.554(2)	140.0
	C(27)—H...N(3)	2.63	3.701(2)	169.9
	C(32)—H...O(4)	2.37	3.406(3)	159.8
	C(18)—H...O(3)	2.75	3.767(2)	155.9
	C(19)—H...Cl(5)	2.87	3.626(2)	127.2
	Cl(5)...Cl(5)		3.773(0)	150.8, 150.8 (I)
	Cl(5)...Cl(6)		3.708(1)	154.5, 106.5 (II)
	Cl(1)...Cl(3)		3.459(1)	160.5, 107.2 (II)
	Cl(2)...Cl(3)		3.611(1)	154.3, 105.9 (II)
2-BrPOT	C(15)—H...N(1)	2.62	3.596(8)	150.1
	C(36)—H...N(6)	2.65	3.630(8)	150.4
	C(8)—H...O(4)	2.59	3.542(8)	146.1
	C(35)—H...O(2)	2.64	3.635(8)	152.7
	Br(3)...Br(5)		3.729(1)	157.6, 91.9 (II)
	Br(1)...Br(5)		3.754(1)	147.3, 99.3 (II)
	C—Br(1)...O(6)		3.514(4)	160.3
2-IPOT	C(10)—H...N(5)	2.65	3.511(4)	135.6
	C(10)—H...N(5)	2.56	3.522(5)	147.7
	C(5)—H...O(3)	2.56	3.513(4)	146.0
	C(35)—H...O(4)	2.69	3.721(4)	158.5
	I(3)...I(2)		3.899(0)	147.4, 94.3 (II)
	I(5)...I(2)		3.823(0)	162.7, 87.5 (II)
	C—I(3)...O(2)		3.544(2)	160.1

^aInter-halogen interactions are classified as type I or type II (Fig. 1). The type II geometry is generally shorter than the type I contact in the same structure.

C–X⋯Cl–M interactions, consistent with the electrostatic L geometry. Fluorine behaves quite differently from the other three halogens because of its hardness, small size, and high electronegativity. Short inter-halogen contacts are a result of close packing due to the elliptical shape of the halogen atom and/or electrophile⋯nucleophile pairing because of mutual polarization. Inter-halogen type I inversion geometry is essentially a manifestation of close packing, whereas directionality of the type II interaction is due to charge polarization of the heavy halogen [14].

Halogen bonding, a term used to describe bonding between the electropositive portion of heavy halogen atom and the negative electron cloud of a heteroatom, is an $n \rightarrow \sigma^*$ type interaction [15]. Its energy varies between 2 and 40 kcal/mol for the weakest Cl⋯Cl contact to the strongest I₂⋯I[−] donor–acceptor interaction [16]. Heteroditopic ligands have been designed by Resnati and coworkers [17,18] in multicomponent assemblies for directing topochemical reactions. We recently showed that the weak C–I⋯O₂N halogen bond exerts a structure-directing influence even in the presence of strong hydrogen bonding groups, for example, the urea α -network and the acid⋯pyridine heterosyn-

thon [19,20]. Halogen bonding also plays an important role in biological recognition, for example, in the binding of thyroxine to its receptor protein [21].

RESULTS AND DISCUSSION

Structural Analysis

We have previously described lattice inclusion structures of 2,4,6-tris(4-halophenoxy)-1,3,5-triazine host for a wide variety of aromatic guests and architectural isomerism of the hexagonal framework from infinite 1D channel (X=Cl) to a finite cavity (X=I), depending on the X group. The chloro host forms 12-Å-diameter channels for guest inclusion whereas the larger iodo group results in a cage cavity of the same dimension; both channel and cage structures were observed in the bromo derivative depending on the guest species [22–27]. We discuss in this paper crystal structures of 2,4,6-tris(2-halophenoxy)-1,3,5-triazine, which do not have microporous cavities but instead organize as close-packed structures. Similarly, 2,4,6-tris(3-halophenoxy)-1,3,5-triazine also crystallize without solvent inclusion [28,29]. These isomeric

TABLE 2 Crystallographic Data on 2-XPOT Compounds

	2-FPOT	2-ClPOT	2-BrPOT	2-IPOT
Empirical formula	C ₂₁ H ₁₂ F ₃ N ₃ O ₃	C ₂₁ H ₁₂ Cl ₃ N ₃ O ₃	C ₂₁ H ₁₂ Br ₃ N ₃ O ₃	C ₂₁ H ₁₂ I ₃ N ₃ O ₃
Formula weight	411.34	460.69	594.07	735.04
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic
Space group	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$
<i>T</i> (K)	298(2)	100(2)	298(2)	100(2)
<i>a</i> (Å)	10.2873(14)	10.5719(9)	12.6081(7)	12.6396(8)
<i>b</i> (Å)	10.4290(14)	10.8569(10)	12.9537(7)	13.1959(9)
<i>c</i> (Å)	10.8937(15)	20.0712(18)	15.6797(9)	15.7765(10)
α (°)	61.934(2)	99.9270(10)	72.3010(10)	71.4550(10)
β (°)	70.098(2)	90.8230(10)	69.5760(10)	68.9180(10)
γ (°)	72.723(2)	115.8400(10)	67.1300(10)	66.9950(10)
<i>Z</i> '	1	2	2	2
<i>Z</i>	2	4	4	4
Volume (Å ³)	956.4(2)	2031.9(3)	2168.7(2)	2211.2(2)
<i>D</i> _{calc} (g/cm ³)	1.428	1.506	1.819	2.208
<i>F</i> (000)	420	936	1152	1368
μ (mm ^{−1})	0.117	0.480	5.608	4.268
θ_{\max}	2.13–26.04	2.07–25.50	1.41–25.50	1.71–25.50
Range <i>h</i>	−12 to 12	−12 to 12	−15 to 15	−15 to 15
Range <i>k</i>	−11 to 12	−12 to 13	−15 to 14	−15 to 15
Range <i>l</i>	−13 to 13	−24 to 24	−18 to 18	−19 to 19
<i>N</i> -total	6860	15603	16946	25999
<i>N</i> -independent	3602	7512	8064	8229
<i>N</i> -observed	2505	6584	4797	7810
<i>R</i> ₁ [<i>I</i> > 2 σ (<i>I</i>)]	0.0429	0.0327	0.0489	0.0217
<i>WR</i> ₂	0.1172	0.0864	0.1327	0.0525
GOF	1.021	1.035	1.042	1.089

compounds are abbreviated as 2-XPOT, 3-XPOT, and 4-XPOT from our previous notation. The specific molecular arrangements (shown in Figs. 2–4) and intermolecular interactions (Table 1) in these X-ray crystal structures (Table 2) are analyzed.

2-FPOT crystallizes in space group $P\bar{1}$ and contains one molecule in the asymmetric unit. The Piedfort Unit dimer (PU) [30–32] is stabilized by $\pi\cdots\pi$ stacking (3.34 Å) and C–H \cdots O and C–H \cdots N interactions from the *ortho*-phenyl donor to the phenoxy-triazine group of the next layer. The *ortho*-halogen on both sides prevents continuous stacks along the PU axis, and so the molecules align with slight offset. One F atom from a PU sits on top of the intramolecular fluoro trimer of the next PU dimer in the column (Fig. 2). The closest F \cdots F distance in the

triangular motif is 3.26 Å, which is greater than the van der Waals sum (2.94 Å) [33]. The stacking axis is inclined to the PU axis along [1–2 2] by 26.6°, unlike in hexagonal packing, where it is perfectly parallel. These tilted columns close-pack to generate the 3D structure.

2-CIPOT crystallizes in space group $P\bar{1}$ with two molecules in the asymmetric unit ($Z' = 2$). The PU dimers between symmetry-related molecules stack similar to 2-FPOT in the tilted columns. These parallel columns arrange in alternate layers of symmetry-independent molecules. The $\pi\cdots\pi$ stacking distance between the triazine rings in PUs is 3.23 and 3.44 Å, such columns are tilted with respect to the PU axis by 20.2° and 20.9°, and the skew angle between the columns is 56.7°. There are Cl \cdots Cl interactions of 3.5–3.7 Å, with a type II interaction

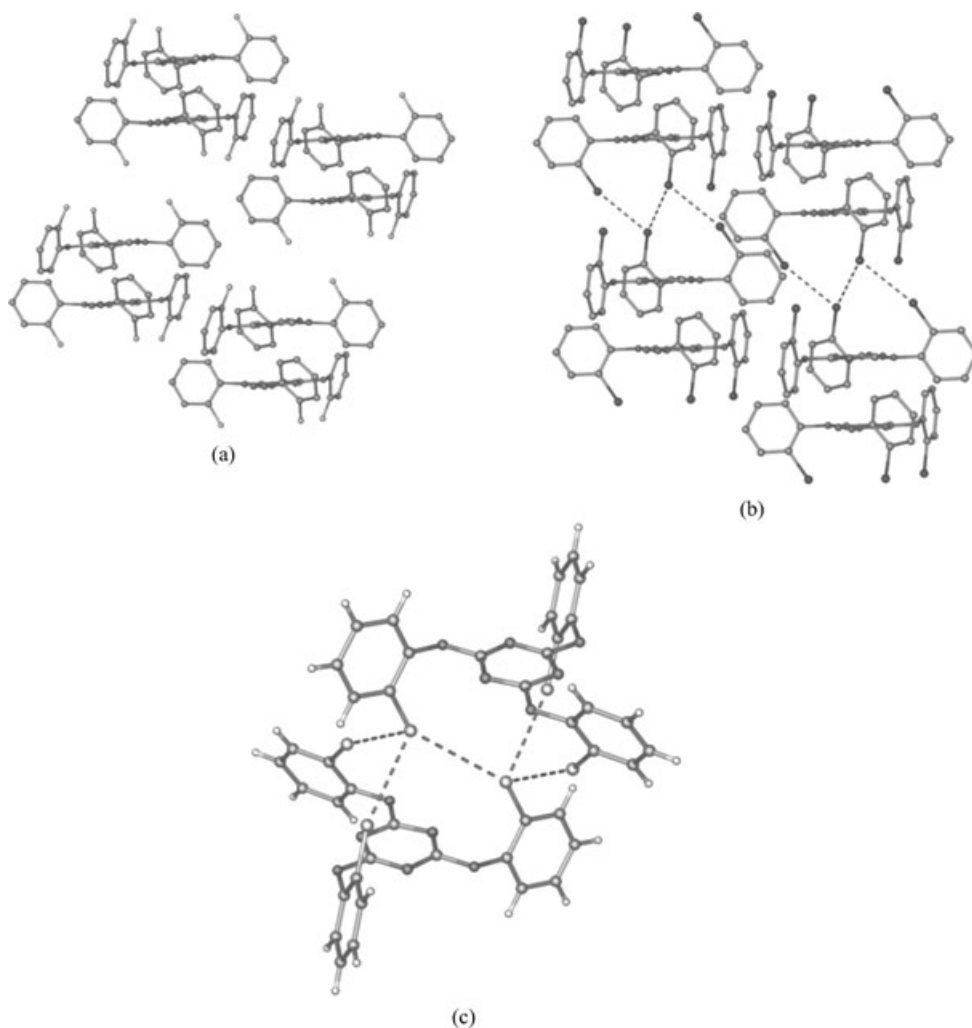


FIGURE 2 2D layers of PU dimers stacked with slight offset in the crystal structure of (a) 2-FPOT and (b) 2-CIPOT. One halogen atom from a PU sits on top of the intramolecular halogen trimer of the next PU in the column. (c) Type I and type II Cl \cdots Cl geometry in 2-CIPOT (see Table 1).

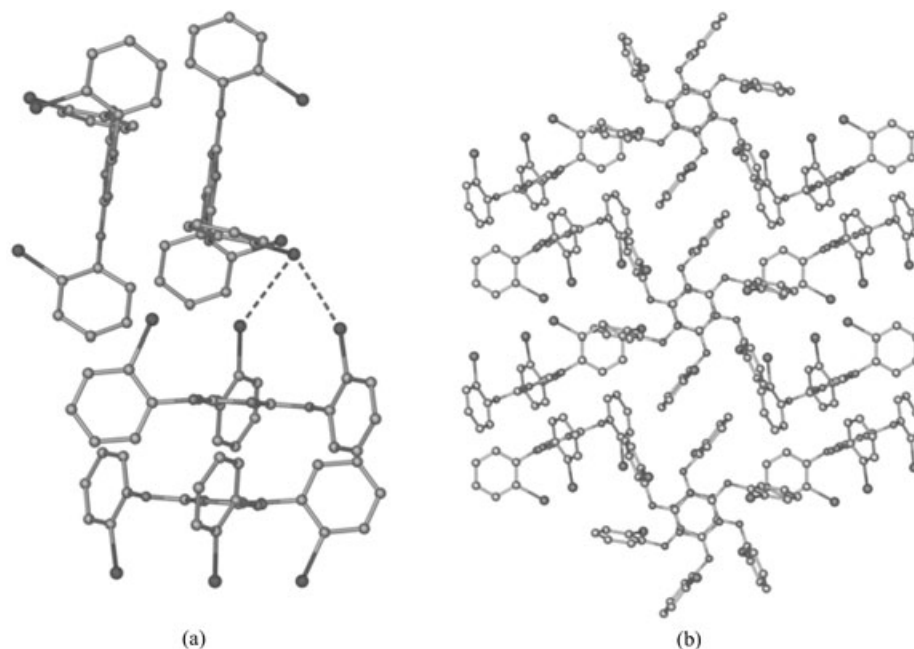


FIGURE 3 (a) Bifurcated inter-halogen interaction of type II geometry in the crystal structure of 2-BrPOT and (b) Piedfort Unit to show the pseudo-hexagonal arrangement. The crystal structure of 2-IPOT is identical.

being the shortest (Table 1). The 2D arrangement in 2-ClPOT is isostructural to 2-FPOT, that is, their layer motifs are identical but there are differences in the 3D molecular arrangement. We have discussed 1D, 2D, and 3D isostructurality in steroid and polycarboxylic acid crystal structures [34–36], and Kálmán et al. have analyzed polymorphic crystal structures at increasing degrees of similarity [37].

2-BrPOT crystallizes with two molecules in the asymmetric unit in space group $P\bar{1}$. Here also similar PUs are observed between symmetry-related molecules and the distance between the triazine planes is 3.46 and 3.62 Å. Symmetry-independent PUs are aligned almost perpendicular (87.2°) because the bromo groups form type II Br \cdots Br contact of 3.73 Å, 157.6° , 91.9° and 3.75 Å, 147.3° , 99.3° (Fig. 3) along with C–Br \cdots O and C–Br \cdots π interactions. 2-IPOT is isostructural to 2-BrPOT and their unit-cell similarity index, $\Pi = 0.008$ [38].* The triazine planes are 3.34 and 3.49 Å apart in the symmetry-independent PUs that are inclined at 87.1°

to each other. The geometry of the type II I \cdots I interaction is 3.90 Å, 147.4° , 94.3° and 3.82 Å, 162.7° , 87.5° together with electrostatic C–I \cdots O and C–I \cdots π interactions in the structure. As the type II interaction approaches the optimal L-geometry, the inter-halogen Br \cdots Br and I \cdots I distances become shorter.

The crystal structures of 3-XPOT compounds were reported previously [28,29]. 3-ClPOT, 3-BrPOT, and 3-MePOT are isostructural in space group $P\bar{3}c1$. This indicates that the halogen group is playing more of a space-filling role. Similar to the packing in guest-free 4-BrPOT [39], these structures have continuous PUs of hexagonal symmetry (Fig. 4). The crystal structure of 3-IPOT (space group $R\bar{3}$) has 1/3 molecule in the asymmetric unit. The molecules are stacked in the C_{3i} -PU as a helix along the c -axis via type II I \cdots I interaction (3.85 Å, 169.9° , 83.0°) because of mutual polarization between the soft iodine atoms. Triazine rings are separated by 3.42 and 3.87 Å in the PU and connected via C–H \cdots O and C–H \cdots N interactions via the *ortho*-H donors whereas the *meta*-H atoms participate in C–H \cdots I interaction. In contrast to differences in 3-XPOT structures, 4-XPOT structures have hexagonal cavities or channels for guest inclusion (X=Cl, Br, I). A slice of the hexagonal layer mediated via the iodo trimer synthon in 4-IPOT host is shown in Fig. 4 [27].

*The unit cell similarity index $\Pi = |(a+b+c) \div (a'+b'+c')| - 1$, where a , b , c and a' , b' , c' are the orthogonalized lattice parameters (Löwdin program) of the isomorphous crystals. $\Pi \cong 0$ indicates identity between crystal structures. If two crystal structures are very different, then Π is not calculated for such pairs. We thank Prof. A. Kálmán and Dr. L. Fábrián (Hungarian Academy of Sciences) for a copy of the program to calculate isostructurality indices.

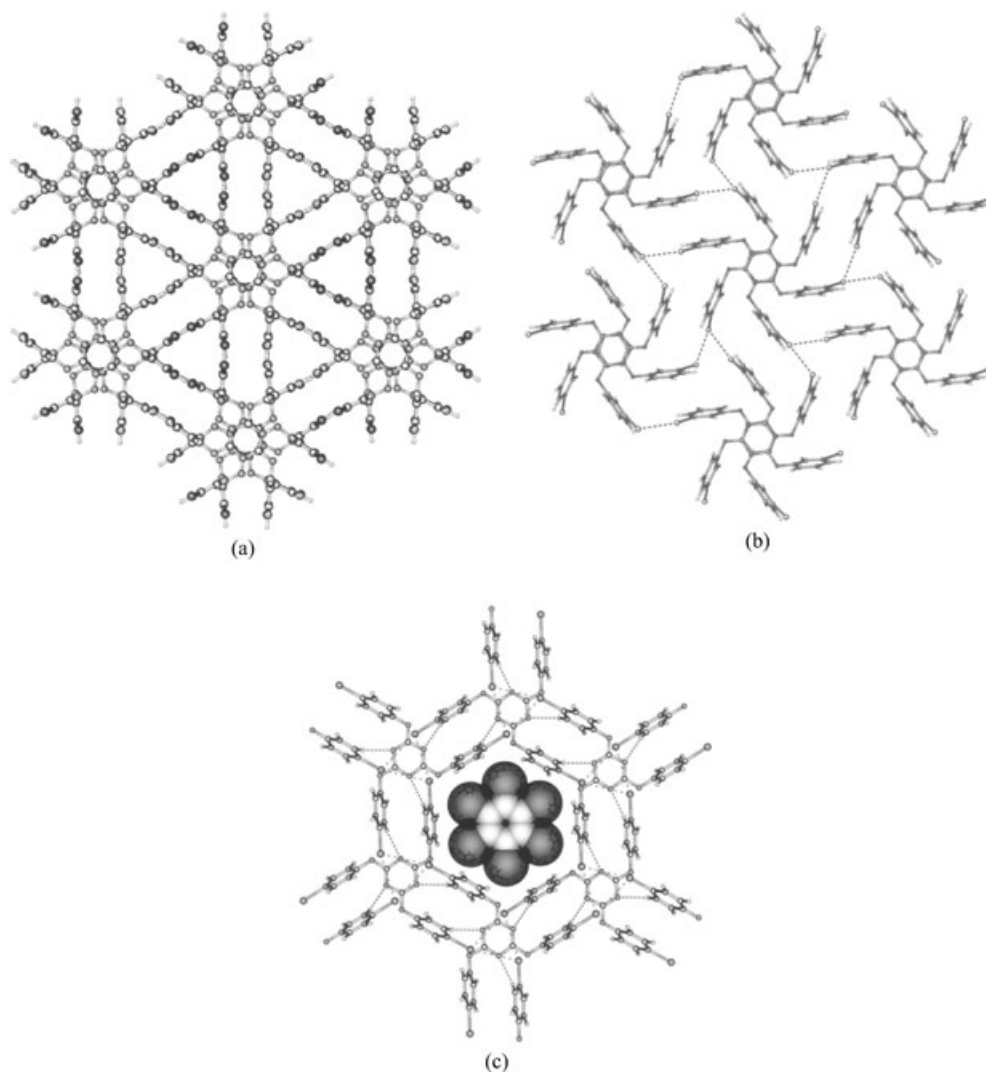


FIGURE 4 (a) Stacked PU column in 3-CIPOT. There are no specific Cl...Cl interactions. 3-BrPOT and 3-MePOT are isostructural. (b) I...I helix and PU column in the structure of 3-IPOT. (c) Hexachlorobenzene guest inclusion in the 12 Å on each side hexagonal cavity of the 4-IPOT host. The cage structure of 4-IPOT has C_{3i} -PU, but π - π stacking is absent in the channel structures of 4-CIPOT and 4-BrPOT. The 2D hexagonal layer is identical in these 4-XPOTs.

Isostructurality in Halogen Compounds

Motherwell and coworkers [40] developed a program GRX (GRoup eXchange) to search crystal structures related by functional group replacement. They analyzed methyl-chlorine and methyl-bromine substitution change in crystal structures. The simulated powder patterns are then compared to check isostructurality in crystal structure pairs. There is isostructural exchange of chlorine or bromine for the methyl group in 26% and 25% cases, indicating that both these halogens are equally effective in replacing a methyl group without changing the crystal packing [40].

A search of the Cambridge Structural Database (CSD version 5.26, February 2005 update) was carried out to determine the frequency of isostructurality in organic halogen compounds (i.e., those containing a Cl, Br or I group) and the probability that the bromo derivative is similar to the chloro or iodo crystal structure was estimated. A subdatabase of crystal structures for which all three halogen derivatives of the same organic compound are reported was prepared manually. Monovalent iodine-containing organic compounds whose 3D coordinate are determined, are single-component, not disordered, and not polymeric; no errors, no ions, no powder structures, and $R < 0.10$ were

TABLE 3 CSD Refcodes of the Same Molecule Having Cl, Br, and I Derivatives^a

No.	Fluoro	Chloro	Bromo	Iodo	Π
1	HUFVEJ	ACOKAE	ACOKEI	ACOKIM	I/Br = 0.029
2		BAXTUQ	BAXVAY	BAXVIG	I/Cl = 0.008
3	BEFSOV	SUHSET	JUKVIU	BEFSUB	I/Br = 0.023 Br/F = 0.068 I/F = 0.093
4	PFBZAD01	CLBZAP01	BRBZAP	BENMOW01	I/Br = 0.074 Br/F = 0.026 I/F = 0.103
5		UGIGEW	BROPOS	BENXAT	Nil
6		TECLPH01	TBPHAN	BOPDOZ	Br/Cl = 0.020
7		CCBCBT	CBBCBT	CIBCBT	I/Br = 0.032
8	VAXLUB	SEGWUW	SEGXAD	DIHRIV	Br/Cl = 0.005
9		DCLMET10	DBRMET10	DIMETH01	I/Br = 0.058
10	BENAFM10	NABRAJ	BRBZAM	DUMNUU	I/Br = 0.017 Br/Cl = 0.010 I/Cl = 0.027
11		CLANIC05	PBRANL01	EJAYET	Br/Cl = 0.026
12	KIFXIG	BENCLN02	BENBRN02	ENIGIR	Br/Cl = 0.0003
13		FABDIW	FABDOC	FABDUI	I/Br = 0.037 Br/Cl = 0.015
14	GOGXOP	GOGXEF	PALWOO	GIHTIA	I/Br = 0.035 Br/Cl = 0.032 I/Cl = 0.068
15	HIRNEB	TIYJEQ01	TIYJIU01	HIRPAZ01	I/Cl = 0.032
16	BIGSUF	CLBZAM10	BRBZAO	IBNZAM	I/Br = 0.017
17		CCACEN	BCACEN	ICACEN	I/Br = 0.057 Br/Cl = 0.029 I/Cl = 0.087
18	FDOURD	CLDOUR	BROXUR10	IDOXUR	Br/Cl = 0.007
19	DFPSLO	CLPSUL01	BPHSUL01	IPSULO	I/Br = 0.018 Br/Cl = 0.022
20		CPPTLM01	BPPHIM	IPTHIM10	I/Br = 0.025 Br/Cl = 0.003 I/Cl = 0.022
21		CUNWIR	UNASOR	IQITIL	Nil
22	FURACL	CLURAC10	BRURAC10	IURACL10	Br/Cl = 0.019
23		CLURID10	BRURID10	IURIDN10	Br/Cl = 0.009
24	TAPSEI	JENHIV	JIKCAH	KEYNUX	Br/Cl = 0.001
25		SINVOA	SINVIU10	KICRET	Br/Cl = 0.009
26		MUTZOQ	MUTZIK	LALMEQ	Br/Cl = 0.003
27		MUVBAG	MUTZUW	LALNUH	Br/Cl = 0.004
28	LIKHOE	LIKHUI	LIKJEU	LIZNEN	Nil
29		LUSNAO	VIXHAL01	LUSNUI	I/Br = 0.023 Br/Cl = 0.031 I/Cl = 0.055
30	NACBUO	NACCEZ	NACCAV	NACBOI	I/Br = 0.019 Cl/F = 0.046
31		NEGJAK	NEGKIT	NEGLEQ	I/Br = 0.021 Br/Cl = 0.009 I/Cl = 0.030
32		NEGJEO	NEGKOZ	NEGLIU	Br/Cl = 0.005
33		NOTZAX	NOTZEB	NOTZIF	I/Br = 0.009 Br/Cl = 0.005 I/Cl = 0.009
34		WIKKUW	WERBAW	NUZNOL	I/Br = 0.009 Br/Cl = 0.005 I/Cl = 0.014
35		IHARAK	QUDHEC	OCOQIG	I/Br = 0.021 Br/Cl = 0.007 I/Cl = 0.028

Continued

TABLE 3 Continued

No.	Fluoro	Chloro	Bromo	Iodo	Π
36		ODAHOQ	QODQUV01	ODAHUW	Br/Cl = 0.003
37	FBENZA	CLBZAC	BRBZAC	OIBZAC	Br/Cl = 0.006
38	PUGPIQ	DCLBIP	HIQQON	PIPROV	I/Br = 0.021 Cl/F = 0.046
39		ZIVLIZ	QOMYIA	QOMYOG	Br/Cl = 0.003
40		CHLSAN	BSALAN	RAVTIR	I/Br = 0.005 Br/Cl = 0.008
41		YICFAR	YICFEV	RIWTOG	Br/Cl = 0.017
42	FLUANA	CLANAC10	VAGTUS	SANZUC	Br/Cl = 0.001 Cl/F = 0.058
43		ZEPDAZ	PUZHIB	SAQZOY	I/Br = 0.052 Br/Cl = 0.020 I/Cl = 0.074
44		DCLANT01	DBANTH01	TECWUT	I/Br = 0.0003
45		ZZZVTY12	TPHMBR01	TEWWEX	Br/Cl = 0.001
46	HEVLAV	VOYMUR	VOYNAY	VOYNEC	I/Br = 0.009 Br/Cl = 0.003 I/Cl = 0.012
47		VICXOU	VUCHAC	VUCHEG	I/Br = 0.012 Br/Cl = 0.006 I/Cl = 0.018
48		WOJXUO	WOJXIC	WOJXOI	Nil
49		CLNIBZ	BRNIBZ	WURTOS	Br/Cl = 0.001
50		XALBER	MALGOV	XALBIV	Br/Cl = 0.019
51		XAXQIW	XAXQOC	XAXQUI	I/Br = 0.007 Br/Cl = 0.013 I/Cl = 0.006
52		YIHQAH	YIHQUB	YIJQAJ	I/Br = 0.015 Br/Cl = 0.006 I/Cl = 0.021
53		CARBTC	CTBROM	ZZZKDW01	Nil
54	HATXIJ	CBENPH	CUZKUD	ZZZOVY01	Cl/F = 0.028 I/Br = 0.043
55	EBICUO	EBIDAV	EBIDEZ	EBIDID	I/Br = 0.009
56		EYISIO	BRACPH02	EYITAH01	I/Br = 0.028

^aIn some cases the *F* derivative is also reported. Unit cell similarity index, Π [38], is calculated for isostructural pairs.

retrieved. Each structure in the iodo subdatabase (the smallest category among three halogens) was then searched for the corresponding bromo and chloro derivative. If the corresponding fluoro compound is known then this entry was added to Table 3. The unit cell similarity index, Π [38], was calculated for pairs of crystal structures.

There are 56 crystal structures wherein chloro, bromo, and iodo derivative of the same compound is reported and out of these the fluoro structure is also known in 21 cases. There is no example wherein all halogen derivatives (F, Cl, Br, I) of the same compound are isostructural. Interestingly, the chloro, bromo, and iodo compounds are isostructural in 17 cases out of 56, which is a large percentage (30%) for organic compounds. In this series, the more polarizable Br and I derivatives display similar packing in 28 pairs (50%). Interestingly,

the Br and Cl substituents show the most frequent isostructurality in 37 examples (66%). There are only four examples where chloro and fluoro compounds are isostructural, for example, methyl 4-halo-1-cubane-carboxylate, 2,2'-dihalobiphenyl, haloanilic acid, and 4,4'-dihalobenzophenone (entries 30, 38, 42, and 54, respectively). There are three entries (30, 38, and 54) where Cl is isostructural to F and I is isostructural to the Br analog. A new finding from our search is that there are at least three examples, (+)-(3*R*,3*aR*,6*R*,7*S*,7*aS*,8*S*)-6-halo-2,3,3*a*,6,7,7*a*-hexahydro-8-methyl-2-oxo-3,6-methano-1-benzofuran-7-yl crotonate, (4-halophenyl)-propionic acid, and 4-halobenzoic acid (entries 2, 3, and 4), wherein the terminal members are isostructural but not the middle ones. For example, the bromo derivative of the crotonate is different from the isostructural chloro and iodo pair, and the

chloro analog of the propiolic acid and benzoic acid structure is different from the other three isostructural members in each case. This last observation is surprising because Kitaigorodskii generalized that “if the end members of a series are isomorphous, the middle ones are always so as well” [41]. These structures should be examined further to check for polymorphism or is it just a few outliers in a statistical distribution? The reader is referred to the CSD [40] for a detailed examination of all crystal structures listed in Table 3.

CONCLUSIONS

Isostructurality is important not only in crystal engineering but also in the related areas of drug design [36], materials science [42], and the holy grail of crystal structure prediction [43]. The question of “whether a particular functional group or position change on a molecule will lead to a similar or different crystal structure” has no definite answer at the present time. One can make an educated guess from the known structural data to forecast how new members in a given series will crystallize but there is no rigorous predictive model to relate the molecular structure diagram to the crystal structure packing. We observe in the X-POT family of structures that there are differences depending on the *ortho*, *meta*, *para*-position of the halogen group. In the 4-XPOT series, Cl, Br and I are isostructural at the 2D honeycomb network level but the 3D molecular arrangement is different for chloro and iodo whereas bromo behaves like one of these depending on the guest species. In the 2-XPOT series, F and Cl are identical only at the 2D layer similarity, and the crystal structures of the Br and I compounds are 3D isostructural. We became aware of the crystal structures of 2-XPOT compounds determined at different temperatures [44] compared to those carried out by us and their structural similarity (morphotropism) [45,46] after the submission of our work. 3-IPOT is different from its lower halogen analogs because of the I⋯I helix. The electrostatic type II inter-halogen interaction is generally shorter than the space-filling type I geometry. The CSD trends on halogen exchange indicate that the Br atom resides in between Cl and I atoms not only in the periodic table but also in terms of its supramolecular behavior based on its frequency for isostructural exchange. We can only speculate that $Z' = 1$ for 2-FPOT but $Z' = 2$ for 2-CIPOT, 2-BrPOT, and 2-IPOT because of specific but weak inter-halogen interactions in the latter structures, analogous to recent observations on C–H⋯O interactions and multiple molecules in the asymmetric unit [47–49].

EXPERIMENTAL

Synthesis

Four millimoles of 2-halophenol and 4 mmol of KOH were dissolved in THF (30 mL) and stirred for 30 min at room temperature. The reaction mixture was cooled to 0°C and then slowly 1 mmol of cyanuric chloride was added and stirred for 1 h at 0°C. After continuing for 48 h at room temperature, the reaction mixture was poured into crushed ice. The thick white precipitate (75% yield) was filtered by vacuum suction and washed with methanol, dried and purified by column chromatography. All compounds showed satisfactory NMR spectra.

2-FPOT: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 7.09 (m, 6H), 7.17 (m, 6H).

2-CIPOT: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 7.39 (d, $J = 8$ Hz, 3H), 7.26 (m, 6H), 7.17 (d, $J = 8$ Hz, 3H), 7.17 (t, $J = 8$ Hz, 3H).

2-BrPOT: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 7.56 (d, $J = 8$ Hz, 3H), 7.29 (t, $J = 8$ Hz, 3H), 7.17 (d, $J = 8$ Hz, 3H), 7.10 (t, $J = 8$ Hz, 3H).

2-IPOT: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ : 7.78 (d, $J = 8$ Hz, 3H), 7.32 (t, $J = 8$ Hz, 3H), 7.13 (d, $J = 8$ Hz, 3H), 6.96 (t, $J = 8$ Hz, 3H).

Crystallization

A solution of the appropriate 2-XPOT compound (200 mg) in 10 mL chloroform afforded diffraction-quality single crystals by slow evaporation of the solvent over 1 week.

X-ray Crystallography

Reflections were collected for single crystals of 2-FPOT, 2-CIPOT, 2-BrPOT, and 2-IPOT on a Bruker SMART APEX CCD area detector system at 298, 100, 298, and 100 K, respectively (Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å). Multiscan absorption correction was applied for 2-XPOT data in SADABS. Structure solution and refinement were performed using SHELXS-97 and SHELXL-97 [50]. Hydrogen atoms were generated at idealized geometries and isotropically refined using the Riding model. Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms was carried out by the full-matrix least-squares refinement method. Crystallographic .cif files (CCDC Nos. 624302–624305) are freely available from www.ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk.

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