

Triclosan

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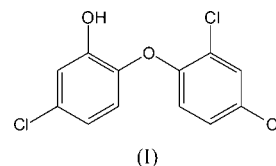
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The title compound [systematic name: 5-chloro-2-(2,4-dichlorophenoxy)phenol], $C_{12}H_7Cl_3O_2$, is a biologically relevant molecule with biocide activity. It crystallizes in the chiral trigonal space group $P3_1$ with one molecule in the asymmetric unit. As in biological adducts, the two aromatic rings are almost mutually perpendicular, with this structural feature leading to a distribution of the pendant $-OH$ groups to maximize the formation of $O-H\cdots O$ hydrogen bonds. This arrangement leads to a chain of molecules running parallel to the c axis and having a $C(2)$ graph-set motif at its core.

Comment

Triclosan [5-chloro-2-(2,4-dichlorophenoxy)phenol], (I), is a broad-spectrum biocide widely employed as an antimicrobial ingredient in household and healthcare-related products. The most common use is in antimicrobial hand soaps, but it can also be found in consumer products such as liquid dishwashing soaps, deodorants and toothpastes at concentrations ranging from 0.15 to 0.3% (Campbell & Zirwas, 2007). Triclosan may also be employed in healthcare at dosages of 1% for use in high-risk high-frequency handwashing (Kampf & Kramer, 2004). The compound features good activity against Gram-positive bacteria and yeasts but is somewhat less active against Gram-negative organisms, and features limited activity against mycobacteria and dermatophytes and little activity against viruses (Regös *et al.*, 1979; Jones *et al.*, 2000). Additionally, there are some triclosan-resistant pathogens, the most well described example being *Pseudomonas aeruginosa* (Russell, 2004). It is highly effective at reducing the spread of infection in the healthcare setting. Triclosan has also been described as a potential inducer of acquired bacterial resistance to biocides, but whether it actually induces resistance in real-world settings remains to be demonstrated (Campbell & Zirwas, 2007; Heath & Rock, 2000). It is, thus, surprising to conclude that the crystal structure of triclosan has never been fully determined to date, as unequivocally confirmed by a search of the Cambridge Structural Database (CSD, Version of November 2008 with three updates; Allen, 2002). In addition, it is also important to emphasize that many of its biological functions (e.g. as an enoyl reductase inhibitor; Roujeinikova *et*

al., 1999; Stewart *et al.*, 1999) seem to be strongly related to its molecular recognition process through, for example, π - π stacking with diazaborine molecules.



In recent years, we have been interested in the use of cyclodextrins as molecular carriers for the delivery of anti-tumoural agents based on organometallic coordination complexes. Because single crystals are very rarely isolated, we have developed a strategy which uses Monte Carlo optimization to derive, from powder X-ray data (either laboratory-scale or from a synchrotron source), reliable structural models of host-guest complexes (Marques *et al.*, 2008, 2009; Pereira *et al.*, 2007, 2008), for which good crystallographic determinations of the guest species need to be available in the literature. More recently, we have focused on the use of biologically active organic molecules, such as the title compound, (I). In this paper, we report the crystal structure of triclosan determined at 150 K.

Compound (I) crystallizes in the chiral space group $P3_1$ with one molecule composing the asymmetric unit (Fig. 1). The two aromatic rings [$C1'-C6'$ (2,4-dichlorophenyl) and $C1-C6$ (4-chloro-2-hydroxyphenyl)] are not coplanar, subtending an angle of $87.98(8)^\circ$. This arrangement minimizes the steric repulsion between spatially close chloro and hydroxyl groups and further promotes π - π stacking in the crystal structure (see below). It is worth emphasizing that this mutual arrangement of the aromatic rings has been previously described for adducts of triclosan with, for example, NADH and diazaborine (Roujeinikova *et al.*, 1999; Stewart *et al.*, 1999), and also in the β -cyclodextrin supramolecular adduct reported by Paulidou *et al.* (2008).

The pendant hydroxyl group is approximately in the average plane of the $C1-C6$ ring (torsion angle $C6-C1-O1-H1 = 11^\circ$), which maximizes the $O-H\cdots O$ hydrogen-bonding interactions between adjacent triclosan molecules (see Fig. 2 and Table 1 for dimensions). These connections are further strengthened by the presence of weak offset π - π stacking interactions between the $C1-C6$ ring (centroid $Cg1$) of one molecule and the $C1'-C6'$ ring (centroid $Cg2$) of the

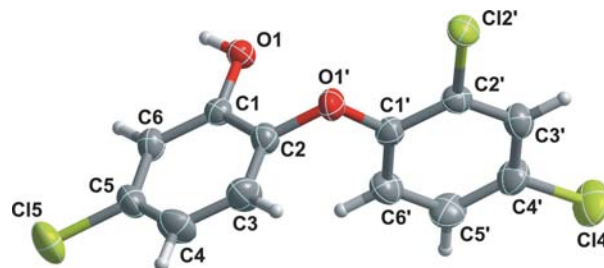
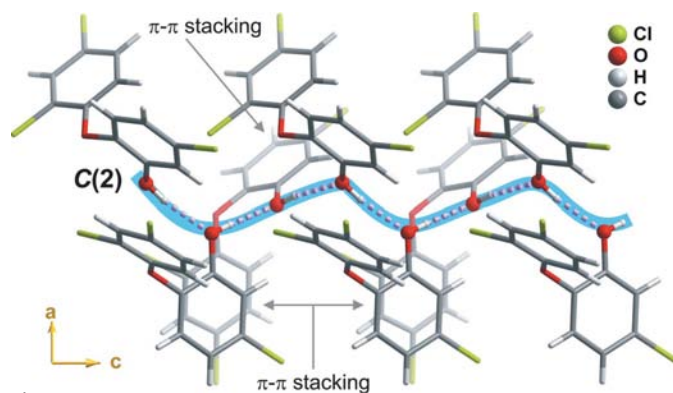


Figure 1

The molecule of triclosan, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 80% probability level and H atoms are shown as small spheres of arbitrary radii.

**Figure 2**

Schematic representation of the O—H...O hydrogen-bonding interactions (dashed lines) connecting adjacent triclosan molecules along the [001] direction of the unit cell, leading to a supramolecular chain described as a $C(2)$ graph-set motif. The presence of π – π stacking interactions between adjacent molecular units is emphasized.

adjacent ring at $(-x + y, -x, -\frac{1}{3} + z)$; the $Cg1 \cdots Cg2$ separation is 3.9156 (9) Å. This co-operative effect between the O—H...O hydrogen bonds and the π – π contacts leads to the formation of a one-dimensional chain having at its core a helix-type $C(2)$ graph-set motif (Bernstein *et al.*, 1995). Individual chains are close-packed in the solid state with only van der Waals contacts between them.

Experimental

Triclosan was purchased from Alfa Aesar (99% purity) and used as received without further purification. Large single crystals suitable for crystallographic studies were isolated over a period of one week by slow evaporation from an ethanolic solution.

Crystal data

$C_{12}H_7Cl_3O_2$	$Z = 3$
$M_r = 289.53$	Mo $K\alpha$ radiation
Trigonal, $P3_1$	$\mu = 0.74 \text{ mm}^{-1}$
$a = 12.5225 (1) \text{ Å}$	$T = 150 \text{ K}$
$c = 6.6809 (1) \text{ Å}$	$0.22 \times 0.08 \times 0.06 \text{ mm}$
$V = 907.29 (2) \text{ Å}^3$	

Data collection

Bruker APEXII X8 KappaCCD diffractometer	35385 measured reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 1997)	5670 independent reflections
$T_{\min} = 0.854$, $T_{\max} = 0.957$	4382 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.044$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.037$	H-atom parameters constrained
$wR(F^2) = 0.070$	$\Delta\rho_{\text{max}} = 0.38 \text{ e Å}^{-3}$
$S = 1.03$	$\Delta\rho_{\text{min}} = -0.28 \text{ e Å}^{-3}$
5670 reflections	Absolute structure: Flack (1983),
155 parameters	with 2729 Friedel pairs
1 restraint	Flack parameter: $-0.02 (3)$

H atoms bound to O and C atoms were located at their idealized positions and included in the final structural model in a riding-motion approximation, with C—H = 0.95 Å and O—H = 0.84 Å, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ or $1.5U_{\text{eq}}(\text{O})$.

Table 1

Hydrogen-bond geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$O1-H1 \cdots O1^i$	0.84	1.97	2.8058 (10)	171

Symmetry code: (i) $-y, x - y, z + \frac{1}{3}$.

Data collection: *APEX2* (Bruker, 2006); cell refinement: *APEX2*; data reduction: *SAINT-Plus* (Bruker, 2005); program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *DIAMOND* (Brandenburg, 2009); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG3111). Services for accessing these data are described at the back of the journal.

References

- Allen, F. H. (2002). *Acta Cryst.* **B58**, 380–388.
- Bernstein, J., Davis, R. E., Shimon, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Brandenburg, K. (2009). *DIAMOND*. Version 3.2. Crystal Impact GbR, Bonn, Germany.
- Bruker (2005). *SAINT-Plus*. Version 7.23a. Bruker AXS Inc., Madison, Wisconsin, USA.
- Bruker (2006). *APEX2*. Version 2.1-RC13. Bruker AXS Inc., Madison, Wisconsin, USA.
- Campbell, L. & Zirwas, M. J. (2007). *Dermatitis*, **17**, 204–207.
- Flack, H. D. (1983). *Acta Cryst.* **A39**, 876–881.
- Heath, R. J. & Rock, C. O. (2000). *Nature (London)*, **406**, 145–146.
- Jones, R. D., Jampani, H. B., Newman, J. L. & Lee, A. S. (2000). *Am. J. Infect. Control*, **28**, 184–196.
- Kampf, G. & Kramer, A. (2004). *Clin. Microbiol. Rev.* **17**, 863–893.
- Marques, J., Anjo, L., Marques, M. P. M., Santos, T. M., Paz, F. A. A. & Braga, S. S. (2008). *J. Org. Chem.* **693**, 3021–3028.
- Marques, J., Braga, T. M., Paz, F. A. A., Santos, T. M., Lopes, M. F. S. & Braga, S. S. (2009). *Biometals*, **22**, 541–556.
- Paulidou, A., Maffeo, D., Yannakopoulou, K. & Mavridis, I. M. (2008). *Carbohydr. Res.* **343**, 2634–2640.
- Pereira, C. C. L., Diogo, C. V., Burgueiro, A., Oliveira, P. J., Marques, M. P. M., Braga, S. S., Paz, F. A. A., Pillinger, M. & Gonçalves, I. S. (2008). *Organometallics*, **27**, 4948–4956.
- Pereira, C. C. L., Nolasco, M., Braga, S. S., Paz, F. A. A., Ribeiro-Claro, P., Pillinger, M. & Gonçalves, I. S. (2007). *Organometallics*, **26**, 4220–4228.
- Regös, J., Zak, O., Solf, R., Vischer, W. A. & Weirich, E. G. (1979). *Dermatologica*, **158**, 72–79.
- Roujeinikova, A., Levy, C. W., Rowsell, S., Sedelnikova, S., Baker, P. J., Minshull, C. A., Mistry, A., Colls, J. G., Camble, R., Stuitje, A. R., Slabas, A. R., Rafferty, J. B., Pauptit, R. A., Viner, R. & Rice, D. W. (1999). *J. Mol. Biol.* **294**, 527–535.
- Russell, A. D. (2004). *J. Antimicrob. Chemother.* **53**, 693–695.
- Sheldrick, G. M. (1997). *SADABS*. Version 2.01. Bruker AXS Inc., Madison, Wisconsin, USA.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Stewart, M. J., Parikh, S., Xiao, G., Tonge, P. J. & Kisker, C. (1999). *J. Mol. Biol.* **290**, 859–865.