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Solid state study of hydrogen bonding in dichlorophen crystals

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Abstract

An X-ray crystallographic study of dichlorophen has been performed. Intramolecular hydrogen bonding is found within the molecule and intermolecular hydrogen bonding is present between molecules. The formation of dimers within the crystal lattice has been established.

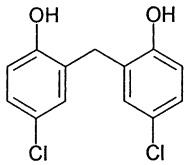
Keywords: Dichlorophen; X-ray crystallography; Hydrogen bonding; Crystals

1. Introduction

Advances in pharmaceutics are related to our understanding of mechanisms and organisations at the molecular level. As most pure drugs are crystalline at room temperature and the tablet remains the most popular dosage form, it is the solid state that is increasingly being examined. When a drug or excipient can be obtained as small, well-formed crystals, the X-ray crystallography technique can yield much information at the molecular level.

The physical properties of crystalline organic drugs are related not only to the individual molecule but also to the packing of the molecules in the crystal. Hydrogen bonding can play a crucial role in such studies as its presence can enhance the rigidity of a desired molecular arrangement and influence physical properties such as melting point and density. Variations in hydrogen bonding can also lead to polymorphism and affect bioavailability. Studies that have compared hydrogen-bonding schemes in organic molecules include work on sulfonamides (Adsmond and Grant, 2001), phenols (Prout et al., 1988) and anticonvulsant enaminones (Kubicki et al., 2000). Theoretical studies on hydrogen bonding in drugs have also been made (Gancia et al., 2001) and the description of hydrogen bonding by use of graph set analysis is well established (Etter et al., 1990). Attempts to gather information on how to predict molecular packing within crystals in relation to polymorphism remains an important feature of preformulation studies. We have now used the single crystal X-ray diffraction technique to establish the molecular features of dichlorophen in the solid state.

Dichlorophen (**1**) is an anthelmintic that is active against species of tapeworm but it use in this area has been superseded by praziquantel or niclosamide (Martindale, 1999). It has antifungal and antibacterial activity and is used to treat fungal infections of the skin. It is present in Mycota® spray (BMA & RPSGB,



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2001) and is used as a germicide in soaps and cosmetics. It is also used as a fungicide in agriculture but its misuse use can have fatal consequences (Kintz et al., 1997) and amateur use of dichlorophen has been banned by the Ministry of Agriculture, Fisheries and Food (MAFF, 1997). A UV spectroscopic assay for dichlorophen tablets is given in the British Pharmacopoeia (2001) and an HPLC method has been reported for dichlorophen–toluene soft gelatine capsules used in veterinary medicine (Shah et al., 1984).

The simple sketch of the dichlorophen molecule (**1**) shows that it may possess a symmetry plane as one-half of the molecule appears to be a mirror image of the other. However, it is possible that the hydrogen-bonding scheme adopted by the hydroxy groups will introduce asymmetry into the molecule. An X-ray crystallographic investigation was, therefore, performed to establish both the conformation of the molecule and the hydrogen-bonding network in the crystal. An earlier crystallographic investigation was abandoned due to a "complex disordered structure" (Flinnt et al., 1950).

2. Materials and methods

Dichlorophen (CAS No. 97-23-4) 95% with a reported mp 168–172 °C was purchased from ALDRICH and recrystallised from water/petroleum ether. X-ray data were collected on a Nonius Kappa CCD diffractometer (For details of data collection and initial processing, see web page: http://www.soton.ac.uk/~xservice/home.htm).

The molecular structure was solved with SIR97 (Altomare et al., 1999) and refined with SHELX97 (Sheldrick, 1998). The molecular plot was obtained with ORTEP-3 (Farrugia, 1997). Details of hydrogen bonding and the crystal packing diagram were obtained with PLATON (Spek, 2001).

Full details of the data collection and structure refinement are given in Table 1.

Table 1
Crystal data and structure refinement for dichlorophen

Empirical formula	$C_{13}H_{10}Cl_2O_2$
Formula weight	269.11
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 4.1932(2) Å; α = 90° b = 13.5493(6) Å; β = 90.724(2)° c = 20.6147(10) Å; γ = 90°
Volume	1171.13(10) Å^3
Z	4
Density (calculated)	1.526 mg/m^3
Absorption coefficient	0.539 mm^{-1}
F(000)	552
Crystal size	0.22 mm × 0.18 mm × 0.02 mm
Theta range for data collection	3.01–27.46°
Index ranges	$-4 \le h \le 5$, $-17 \le k \le 15$, $-26 \le l \le 26$
Reflections collected	8539
Independent reflections	2658 [R(int) = 0.0407]
Completeness to theta = 27.46°	98.8%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2658/2/184
Goodness-of-fit on F^2	1.002
Final R indices [$I > 2$sigma(I)]	$R1 = 0.0400$, $wR2 = 0.0923$
R indices (all data)	$R1 = 0.0679$, $wR2 = 0.1029$
Largest diff. peak and hole	0.300 and −0.306 e Å^{-3}

3. Results and discussion

The intramolecular hydrogen bond in dichlorophen is shown as a dotted line in a plot of the molecule (Fig. 1). Here the two hydroxy groups are linked together with O1 acting as the donor atom and O2 acting as the acceptor atom. This results in the formation of an eight-membered ring within the molecule

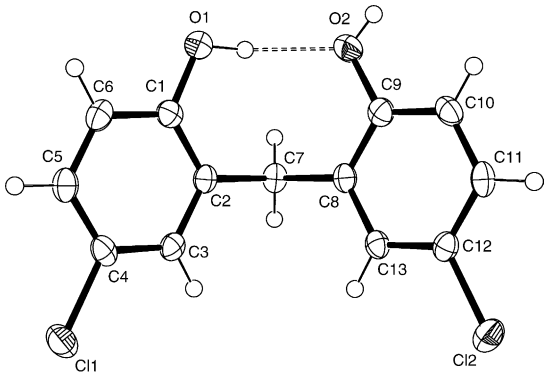

Fig. 1. The atomic arrangement in dichlorophen. Thermal ellipsoids shown at the 50% probability level.

Table 2
Hydrogen bonding in dichlorophen

D–H···A	Type	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
O1–H1···O2	Intramolecular	0.90(2)	1.89(2)	2.740(2)	157(3)
O2–H2···O1[a]	Intermolecular	0.82(2)	2.01(2)	2.782(2)	158(2)

[a] Atom coordinates transformed by $1-x, 1-y, 1-z$.

designated as S(8) by graph set analysis. The tetrahedral angle C2–C7–C8 is 114.2(1)° and there is a slight twist between the aromatic rings as the non-bonded separations C1···C9 = 3.808(3) Å and C3···C13 = 3.696(3) Å only differ by a small amount.

Both the intra- and intermolecular hydrogen bonding is shown as dotted lines in the crystal packing diagram (Fig. 2).

Between each pair of molecules, the hydrogen-bonding motif consists of an eight-membered ring containing four oxygens and four hydrogens. Each oxygen atom acts as both a hydrogen bond donor and a hydrogen bond acceptor in this formation of dimers within the crystal. As there are four donors and four acceptors in this ring, it may be designated $R_4^4(8)$.

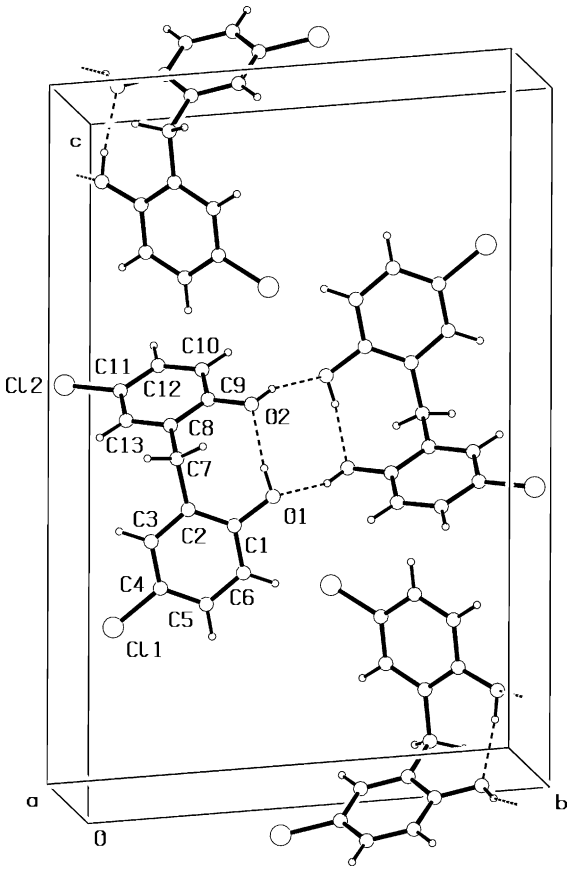

Fig. 2. Dimer formation in the crystal.

Intra- and intermolecular hydrogen bonding exists in other pharmaceutical molecules such as salsalate (Cox et al., 2000) and monocarboxylic acids, such as ibuprofen (Shankland et al., 1997), often exist as dimers in the solid state.

Details of the hydrogen bond geometries are given in Table 2.

Details of atom coordinates, bond lengths, valency angles and torsion angles for dichlorophen have been deposited with the Cambridge Data Centre as supplementary publication no. CCDC 178803. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

4. Conclusion

The X-ray crystallographic study of dichlorophen has established the conformation of the molecule, determined the hydrogen-bonding scheme and has shown that discrete dimers exist within the crystal lattice.

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