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Hydrogen bonding in salicylsalicylic acid (salsalate) crystals

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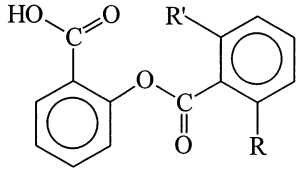
Abstract

An X-ray crystallographic study of the drug salicylsalicylic acid (salsalate) has been performed. Crystal formation of the drug is influenced by both inter- and intra-molecular hydrogen bonding. In addition an OH group in salsalate can occupy alternate *ortho* positions resulting in two hydrogen bonding motifs within a single crystal.

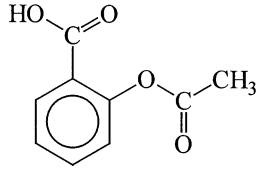
Keywords: Salsalate; X-ray crystallography; Hydrogen bonding; Crystals

1. Introduction

Salicylsalicylic acid (1) is a non-steroidal anti-inflammatory drug (NSAID) with the generic name Salsalate and proprietary preparations available include Disalcid, Disalgesic, Umbradol and Mono-Gesic. It is used to reduce pain and inflammation in conditions such as arthritis, joint pain or muscle strains (Atkinson et al., 1995; Martindale, 1996) and has been reported to be better tolerated than other NSAIDs (Ross, 1991). It is believed to be a possible condensation product (Roth et al., 1991) in the synthesis of aspirin (2) and along with salicylic acid and acetylsalicylsalicylic acid it is one of the major degradation products of aspirin (Blondino and Byron, 1995).



(1)



(2)

The hydroxy group [R or R′ in (1)] occupies the *ortho* position on an aryl ring and its location at either R or R′ may be influenced by possible formation of intramolecular hydrogen bonds. The protonated form investigated here will become deprotonated under physiological conditions but both inter- and intramolecular hydrogen bonds may exist in the solid state. An X-ray crystallographic analysis was therefore performed to establish the position of the hydroxy group on the aryl ring and to determine the hydrogen bonding network in the drug crystal.

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Hydrogen bonding (Jeffrey and Saenger, 1991; Bernstein et al., 1995) is widespread and has been examined by a variety of techniques such as IR spectroscopy, Raman spectroscopy and NMR spectroscopy (Dziembowska, 1994; Brzezinski et al., 1997; Brunner and Sternberg, 1998) but single crystal X-ray diffraction offers the best laboratory-based technique for the determination of hydrogen bonding in light-atom crystalline structures (Taylor and Kennard, 1984; Lommerse et al., 1997). The hydrogen bonds lengths (e.g. C–H, O–H) obtained from X-ray diffraction studies tend to be somewhat less accurate (shorter) than those obtained from neutron diffraction due to the centre of electron density not coinciding with the exact centre of the hydrogen nucleus.

Table 1
Crystal data and structure refinement

Empirical formula	$C_{14}H_{10}O_5$
Formula weight	258.22
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*Fdd*2
Unit cell dimensions	
	$a = 12.9610(5)$ Å
	$b = 28.3230(6)$ Å
	$c = 12.9410(7)$ Å
	$\alpha = 90°$
	$\beta = 90°$
	$\gamma = 90°$
Volume	4750.6(3) Å^3
Z	16
D_{calc}	1.444 Mg m^{-3}
Absorption coefficient	0.111 mm^{-1}
$F(000)$	2144
Crystal size	$0.35 \times 0.25 \times 0.20$ mm
Theta range for data collection	2.34–26.39°
Index ranges	$-16 \leq h \leq 16$
	$-35 \leq k \leq 35$
	$-16 \leq l \leq 16$
Reflections collected	18 431
Independent reflections	2451 [$R_{int} = 0.0597$]
Reflections observed [$(I > 2\sigma(I)$]	2220
Refinement method	Full-matrix least-squares on F^2
Number of parameters	195
Goodness-of-fit on F^2 (S)	1.044
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0392$, $wR_2 = 0.0895$
R indices (all data)	$R_1 = 0.0451$, $wR_2 = 0.0929$
Final weighting scheme: calc $w = 1/[\sigma^2(F_o^2) + (0.0459P)^2 + 4.2161P]$ where $P = (F_o^2 + 2F_c^2)/3$	
Absolute structure parameter	0.1(10)
Residual diffraction max.	0.145 e Å^{-3}
Residual diffraction min.	−0.180 e Å^{-3}

2. Materials and methods

Salicylsalicylic acid [CAS no. 552-94-3] 99% with a reported mp 139–151°C was purchased from ACROS organics (Fisher Scientific) and recrystallised from chloroform. X-ray data were collected on a Nonius Cappa CCD diffractometer (For details of data collection and processing see web page: http://www.soton.ac.uk/ ~ xservice/strat.htm).

The molecular structure was solved with SIR92 (Altomare et al., 1994) and refined with SHELX-97 (Sheldrick, 1998). Tests for tetragonal symmetry (a and c cell lengths are very similar) were performed but the symmetry was found to be orthorhombic (Spek, 1998). Molecular plots were obtained with ZORTEP (Zsolnai, 1997).

Crystal data (Table 1) were collected at low temperature and the structure refined in an orthorhombic space group.

3. Results and discussion

Within the crystal it was found that for 72% of the molecules the hydroxy group occupied one of the two *ortho* positions and in the remaining 28% of the molecules the hydroxy group occupied the alternate *ortho* position. The two possible configurations result in atropisomerism (Cox, 1993). The major configuration (O5, H5A) is shown in Fig. 1 and the minor configuration (O5′, H5B) is shown in Fig. 2. Free rotation about the C8–C9 bond was prevented because the *ortho* hydroxy group formed either a single

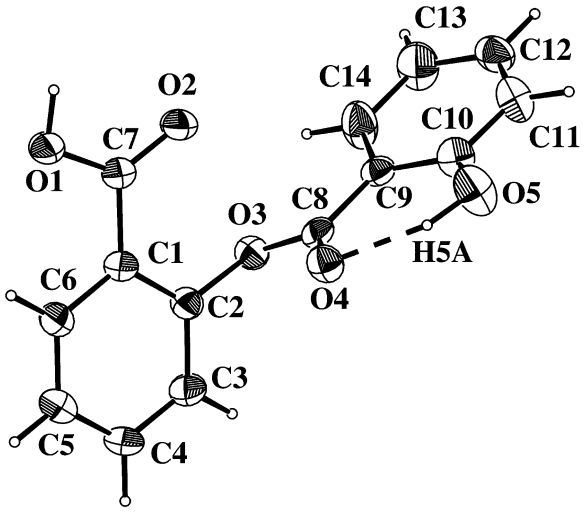

Fig. 1. The atomic arrangement in the major configuration. Thermal ellipsoids shown at the 50% probability level.

intramolecular hydrogen bond with O4 or two intramolecular hydrogen bonds with O3 and O2. The intramolecular hydrogen bonds are shown as dotted lines in the Figures with the bifurcated hydrogen bonds in-volving H5B in the minor configuration. An intermolecular hydrogen bond is also present and full details of these hydrogen bonds are given in Table 2. The distances and angles indicate a strong intermolecular hydrogen bond [O1–H1…O2*], strong intramolecular hydrogen bonds [O5–H5A…O4 and O5′–H5B…O3] and a weak intramolecular hydrogen bond [O5′–H5B…O2]. The strongest intramolecular hydrogen bond is found in the major configuration.

Crystallographic data (excluding structure factors) for salsalate have been deposited with the Cambridge Data Centre as supplementary publication no. CCDC 117404. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail deposit@ccdc.cam.ac.uk).

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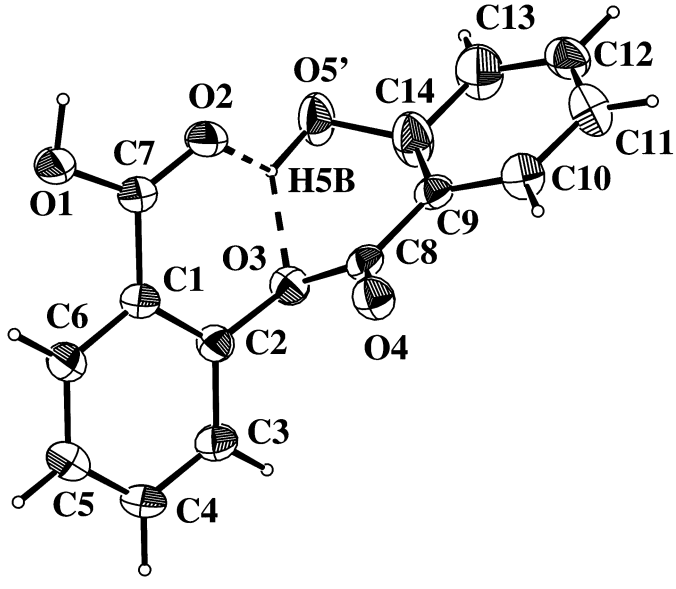

Fig. 2. The atomic arrangement in the minor configuration. Thermal ellipsoids shown at the 50% probability level.

Table 2
Hydrogen bonding in salicylsalicylic acid

D–H…A	Type	D–H (Å)	H…A (Å)	D…A (Å)	D–H…A (°)
O1–H1…O2[a]	Inter	0.93(3)	1.72(3)	2.635(2)	167(3)
O5–H5A…O4	Intra	0.94(6)	1.73(6)	2.614(3)	156(5)
O5′–H5B…O2	Intra	1.08(11)	2.39(10)	3.113(6)	123(7)
O5′–H5B…O3	Intra	1.08(11)	1.77(11)	2.659(6)	136(8)

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

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