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Hydrogen bonds in the crystal packings of mesalazine and mesalazine hydrochloride[1]

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Abstract

The crystal structures of pharmaceutical product mesalazine (marketed also under different proprietary names as Salofalk, Asacol, Asacolitin, and Claversal) and its hydrochloride are reported. In the crystal mesalazine is in zwitterion form as 5-ammoniosalicylate (**1**) whereas mesalazine hydrochloride crystallizes in an ionized form as 5-ammoniosalicylium chloride (**2**). Compound **1** ($C_7H_7O_3N$) crystallizes in the monoclinic space group $P2_1/n$ with $a=3.769(1)$ Å, $b=7.353(2)$ Å, $c=23.475(5)$ Å, $\beta=94.38(2)°$, $V=648.7(8)$ Å^3, $Z=4$, $D_c=1.568$ g cm^{-3} and $\mu(MoK\alpha)=1.2$ cm^{-1}. Compound **2** ($C_7H_8O_3NCl$) crystallizes in the triclinic space group $P\bar{1}$ with $a=4.4839(2)$ Å, $b=5.7936(2)$ Å, $c=15.6819(5)$ Å, $\alpha=81.329(3)°$, $\beta=88.026(3)°$, $\gamma=79.317(4)°$, $V=395.74(3)$ Å^3, $Z=2$, $D_c=1.591$ g cm^{-3} and $\mu(CuK\alpha)=40.8$ cm^{-1}. The crystal structures were solved by direct methods and refined to $R=0.041$ for **1** and 0.028 for **2**, using 607 and 1374 observed reflections, respectively. The configuration of both molecules, with the ortho hydroxyl to a carboxyl group, favours the intramolecular hydrogen bonds. Very complex systems of intermolecular hydrogen bonds were observed in both crystal packings. They are discussed in terms of graph-set notation. The mesalazine crystal structure is characterized by two-dimensional network of hydrogen bonds in the *ab* plane. The crystal structure pattern of mesalazine hydrochloride is a three-dimensional network significantly supported by N^+–H···Cl^- interactions. © 1997 Elsevier Science B.V.

Keywords: Bacteriostatic; X-ray crystallography; Mesalazine crystal structure; Hydrogen bonds

1. Introduction

Among the salicylates, aspirin (acetylsalicylic acid) is the most widely prescribed analgesic–antipyretic and antiinflammatory agent. Some of its derivatives such as 4- and 5-aminosalicylic acids exhibit antimicrobial activity [1]. 4-Aminosalicylic acid is highly specific bacteriostatic effective against *M. tuberculosis*. However, the high and permanent concentration required to be present in human body makes it less applicable than either streptomycin, isomiazid, or rifampin. However, 5-aminosalicylic acid (mesalazine) is used for the maintenance of remission of ulcerative colitis in patients unable to tolerate sulphasalazine, and to cure Crohn's disease. Sulphasalazine, a sulphonamide, has been widely used for treatment of ulcerative colitis, Crohn's disease, and rheumatoid arthritis. It is important to note that degradation of

[1] Dedicated to Prof. George Zundel on the occasion of his 65th birthday.

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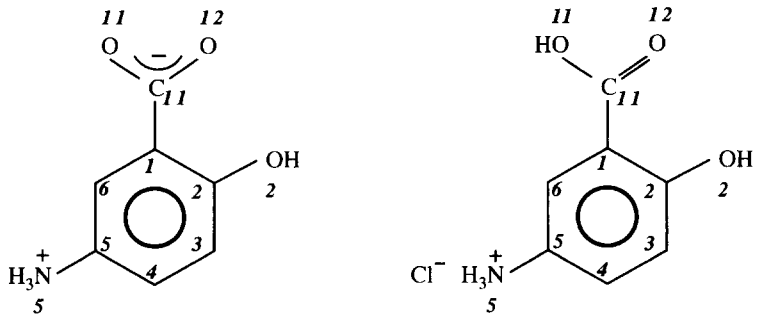

5-ammoniosalicylate (**1**) 5-ammoniosalicylium chloride (**2**)

Scheme 1. Chemical diagrams of **1** and **2**.

sulphasalazine by bacteria in the colon gives mesalazine and sulphapyridine. Thus, mesalazine is an active component in ulcerative colitis but not in rheumatoid arthritis. Although these simple drugs have been so widely in use for quite a time, the crystal structure of 5-aminosalicylic acid has not been reported yet. The present paper deals with the crystal structures of mesalazine and its hydrochloride (Scheme 1), particularly with the hydrogen bond patterns. The literature search using Cambridge Structural Database [2] was used to offer more evidence of N–H···Cl interactions.

2. Experimental

2.1. Crystallizations

The crystals suitable for X-ray structure analysis were selected from the preparations described hereafter.

2.1.1. The crystals of **1**

4.0 g (0.026 mol) of 5-aminosalicylic acid was added to 800 mL of water + acetone mixture (3:1 vol) using deionized water. The suspension was heated at 70°C and clear solution was obtained. To the solution activated charcoal (0.2 g) and sodium hydrosulphite (0.1 g) were added and stirred at 70°C for 15 min. By filtration, the pale yellow solution was obtained and slowly cooled down over 24 h. The crystals were collected by filtration, washed with acetone (50 mL) and dried in air.

2.1.2. The crystals of **2**

20.0 g (0.131 mol) of aminosalicylic acid was dissolved in 200 mL of hydrochloric acid (0.167 mol) using deionized water and the solution was heated up to 55°C. To the dark red solution, activated charcoal (1.0 g) and sodium hydrosulphite were added and stirred at 50–55°C for 15 min. By filtration, the pale yellow solution was obtained and 31.8 mL of hydrochloric acid (36.2%) was added dropwise at 50–55°C over 15 min. The white crystals were collected by filtration of this solution. They were washed two times with acetone (20 mL) and dried at 50°C in vacuo. The yield was 76%.

2.2. Crystal structure determination

Table 1 summarizes crystal data and experimental details of data collection and refinement. Intensities for **1** and **2** were measured on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromatized Mo$K\alpha$ radiation for **1** and Cu$K\alpha$ radiation for **2** using $\omega/2\Theta$ scan mode. The intensity controlled reflections were used each hour for **1** and 2 h for **2** whereas the crystal orientation was checked with two standard reflections each hundred reflections. There were no significant variations in intensity for standard reflections. The data were corrected for Lorentz and polarization effects using the program HELENA [3]. The structures were solved by the SHELXS 86 [4] program and refined on F^2 using the SHELXL 93 [5] program. The H-atom coordinates were located from the subsequent difference Fourier synthesis. Atomic

Table 1
Crystal data and summary of experimental details for compounds **1** and **2**

	1	**2**
Molecular formula	$C_7H_7O_3N$	$C_7H_8O_3NCl$
M_r	153.1	189.6
Crystal size (mm)	0.08 × 0.06 × 0.22	0.11 × 0.07 × 0.22
Data collection		
λ (Å)	0.71073 (Mo$K\alpha$)	1.54184 (Cu$K\alpha$)
T (K)	295(3)	295(3)
No. of reflections for cell determination	22	25
θ range for cell determination (°)	9.8–18.5	40–46
θ range for intensity measurements (°)	2.61–26.32	2.85–74.33
hkl range	0, 4; 0, 9; −29, 29	0,5; −7, 7; −19, 19
Scan	$\omega/2\Theta$	$\omega/2\Theta$
No. of measured reflections	1650	1834
No. of simm. indep. reflections	1106	1619
No. of refl. with $I > 2\sigma(I)$	607	1374
Crystal data		
a (Å)	3.769(1)	4.4839(2)
b (Å)	7.353(2)	5.7936(2)
c (Å)	23.475(5)	15.6819(5)
α (°)	90.0	81.329(3)
β (°)	94.38(2)	88.026(3)
γ (°)	90.0	79.317(4)
V (Å^3)	648.7(8)	395.74(3)
Crystal class and space group	monoclinic, P $2_1/n$	triclinic, P $\bar{1}$
Z	4	2
ρ (g cm^{-3})	1.568	1.591
μ (cm^{-1})	1.2	40.8
F (000) (electrons)	320	196
Solution and refinement		
No. of parameters	128	141
$R_1(F)$ for $F_o > 4\sigma(F_o)$	0.0414	0.0275
$R_1(F)$ for all reflections	0.1254	0.0401
$wR_2(F^2)$ for all reflections	0.1076	0.0834
S for all reflections	0.884	1.046
$\Delta\rho_{max}$ (e Å^{-3}), $\Delta\rho_{min}$ (e Å^{-3})	0.20, −0.19	0.29, −0.23

scattering factors and anomalous dispersion values for chlorine were those included in SHELXL 93 [5]. Details of the refinement procedures are given in Table 1. The molecular geometries were calculated by the program EUCLID [6]. Drawings were prepared by the program PLUTON [6] incorporated in EUCLID and ORTEP [7]. The final atomic coordinates and equivalent isotropic thermal parameters are listed in Table 2 for **1** and Table 3 for **2**. Calculations were performed on Silicon Graphics, INDIGO-2 computer of the X-ray Laboratory, Rudjer Bošković Institute, Zagreb, Croatia.

3. Results and discussion

The structures of **1** and **2** with the atom numbering are shown in Figs. 1 and 2; the ORTEP drawings [7] were prepared with displacement ellipsoids at the 50% probability level. Bond lengths and angles are listed in Table 4. In the crystalline state mesalazine (**1**) is zwitterion whereas mesalazine hydrochloride (**2**) is in ionized form. The geometry of carboxyl group in **1** (Table 4) reveals its deprotonation. In the structure of **2** the carboxyl group, with the torsion

Table 2
Final atomic coordinates and equivalent isotropic displacement parameters (Å^2) with e.s.d.'s (in parentheses) of the non-hydrogen atoms for **1**

Atom	*x/a*	*y/b*	*z/c*	U^a_{eq}
O2	0.5747(6)	0.2909(3)	0.20501(9)	0.0463(7)
O11	0.4687(5)	0.1960(3)	0.03039(8)	0.0417(7)
O12	0.6685(6)	0.1008(3)	0.11628(8)	0.0421(7)
N5	0.0441(7)	0.8457(3)	0.06029(10)	0.0336(8)
C1	0.4166(7)	0.3949(3)	0.10920(10)	0.0235(8)
C2	0.4433(7)	0.4212(4)	0.16837(10)	0.0300(9)
C3	0.3342(8)	0.5844(4)	0.19126(10)	0.0391(10)
C4	0.2033(8)	0.7216(4)	0.15642(10)	0.0340(10)
C5	0.1796(6)	0.6973(3)	0.09771(10)	0.0253(8)
C6	0.2830(7)	0.5364(3)	0.07428(10)	0.0254(8)
C11	0.5259(7)	0.2203(3)	0.08325(10)	0.0294(9)

[a] $U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a_i} \cdot \mathbf{a_j}$.

angle O=C–O–H, reveals a synplanar conformation (Fig. 2). Its geometry (Table 4) is in agreement with data reported for the average bond lengths and angles obtained from neutron diffraction data [C=O ⟨1.21⟩ Å, C–O(H) ⟨1.31⟩ Å, ∠O=C–O–H ⟨123⟩°] [8]. In both structures, bond C5–N5 lengthening is related with an ammonium cation [9]. The rotation of carboxyl group from the plane of aromatic ring is quantified by, e.g. the torsion angle C6–C1–C11–O11[–6.1(4)° for **1** and 3.2(2)° for **2**]. The dihedral angles between the planes of carboxyl group and aromatic ring are 173.7(2)° for **1** and –175.08(5)° for **2**.

3.1. Crystal packing

Very complex systems of intermolecular hydrogen bonds were found in both crystal packings (Table 5 and Table 6). They are described by graph-set notation [10]. The mesalazine crystal structure (**1**) is characterized by a two-dimensional network of N–H···O(carboxylate) hydrogen bonds in the *ab* plane (Fig. 3(a) and (b)). The crystal structure pattern of **2** is a three-dimensional network significantly supported by N^+–H···Cl^- hydrogen bonds (Fig. 4(a) and Fig. 4(b)). The configuration of both molecules, with the ortho hydroxyl to carboxyl group, favours an intramolecular hydrogen bond, detected in both structures (Figs 3(a), 4(a), 5 and 6(a)).

3.1.1. Hydrogen bond pattern of **1**

The intramolecular hydrogen bond between hydroxyl and carboxylato group forms a six-membered

Table 3
Final atomic coordinates and equivalent isotropic displacement parameters (Å^2) with e.s.d.'s (in parentheses) of the non-hydrogen atoms for **2**

Atom	*x/a*	*y/b*	*z/c*	U^a_{eq}
O2	0.9157(3)	0.0036(2)	0.08700(8)	0.0456(4)
O11	0.3792(3)	–0.5184(2)	0.11743(7)	0.0395(4)
O12	0.6728(3)	–0.3139(2)	0.03071(7)	0.0449(4)
N5	0.4223(4)	–0.2537(3)	0.41009(8)	0.0335(4)
C1	0.6199(3)	–0.2495(3)	0.17617(9)	0.0285(4)
C2	0.7926(4)	–0.0679(3)	0.16343(10)	0.0312(4)
C3	0.8417(4)	0.0471(3)	0.23247(10)	0.0332(5)
C4	0.7200(4)	–0.0159(3)	0.31209(10)	0.0302(4)
C5	0.5526(3)	–0.1973(3)	0.32445(9)	0.0273(4)
C6	0.5009(3)	–0.3147(3)	0.25830(9)	0.0283(4)
C11	0.5602(4)	–0.3634(3)	0.10221(9)	0.0317(4)
Cl	0.12971(9)	0.28098(7)	0.43343(2)	0.0381(1)

[a] $U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a_i} \cdot \mathbf{a_j}$.

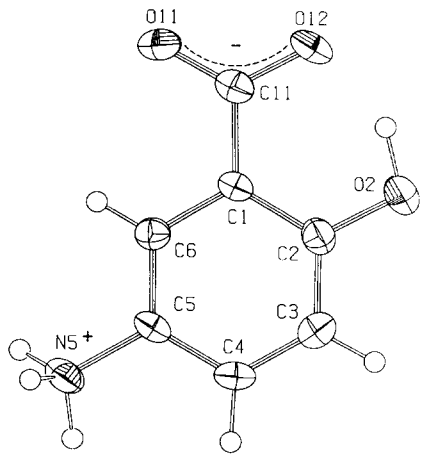

Fig. 1. ORTEP drawing of **1**.

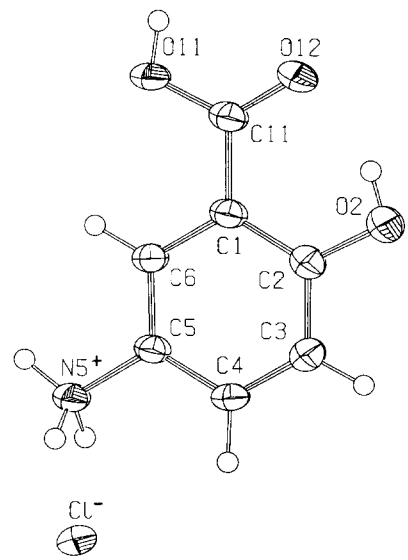

Fig. 2. ORTEP drawing of **2**.

Table 4
Bond distances (Å) and angles for **1** and **2**

	1	**2**
Bond distances (Å)		
O2–C2	1.356(3)	1.343(2)
O11–C11	1.256(2)	1.309(2)
O12–C11	1.264(3)	1.230(1)
N5–C5	1.468(3)	1.462(1)
C1–C2	1.398(3)	1.405(2)
C1–C6	1.395(3)	1.4025(8)
C1–C11	1.492(3)	1.473(2)
C2–C3	1.390(4)	1.397(2)
C3–C4	1.367(4)	1.371(2)
C4–C5	1.386(3)	1.388(2)
C5–C6	1.374(3)	1.371(2)
Angles (°)		
C2–C1–C6	118.4(2)	119.6(1)
C2–C1–C11	121.5(2)	119.20(9)
C6–C1–C11	120.0(2)	121.2(1)
O2–C2–C1	121.8(2)	123.2(1)
O2–C2–C3	118.0(2)	117.2(2)
C1–C2–C3	120.2(2)	119.7(1)
C2–C3–C4	120.7(2)	120.1(2)
C3–C4–C5	119.5(3)	119.9(1)
N5–C5–C4	119.5(2)	117.6(1)
N5–C5–C6	119.8(2)	120.7(1)
C4–C5–C6	120.7(2)	121.60(9)
C1–C6–C5	120.5(2)	119.1(1)
O11–C11–O12	122.7(2)	122.5(1)
O11–C11–C1	119.6(2)	115.83(7)
O12–C11–C1	117.7(2)	121.7(2)

ring [$S(6)$] (Fig. 3(a) and Fig. 5). Intermolecular hydrogen bonds act between ammonium group and carboxylato group (Table 5 and Fig. 3(a)); at N–H52 a three-centered geometry is present. Two interconnected infinite two-dimensional layers related by an inversion symmetry operation are formed parallel to the *ab* plane (Fig. 3(b)). Two characteristic motifs can be recognized: $R_2^2(14)$ and $C(7)$ (Fig. 5). A fourteen-membered ring structure [$R_2^2(14)$] (Fig. 5) is realized between two molecules related by an inversion symmetry operation. The structurally identical dimer patterns, including as donors H51 and H52, are encountered (Fig. 5). Two $C(7)$ chains are detected with the donor participations of H52 and H53 (Fig. 5).

3.1.2. Hydrogen bond pattern of **2**

An intramolecular hydrogen bond of the same type as in **1** forms a six-membered ring [$S(6)$] (Figs 4(a) and 6(a)). The hydrogen bond of the O–H···O type is also involved in the formation of dimers including hydroxyl···hydroxyl interaction [$R_2^2(4)$] and carboxyl···carboxyl group contacts [$R_2^2(8)$] (Figs 4(a) and 6(b)), the most commonly observed motif in the solid state [2]. These two ring structures are interlinked via intramolecular hydrogen bond O2–H2···O12 into a zig–zag chain [$C(8)$] (Figs 4(a) and

Table 5
Hydrogen bond geometry for **1**

	D···*A* (Å)	*D*–H (Å)	H···*A* (Å)	*D*–H···*A* (°)	Symm. op. on *A*
O2–H2···O12 (intra)	2.555(2)	1.04(3)	1.60(3)	150(3)	*x*, *y*, *z*
N5–H51···O11	2.781(3)	0.95(3)	1.87(3)	161(3)	$-x, -y+1, -z$
N5–H52···O11	2.932(3)	0.97(4)	2.28(4)	124(3)	$-x+1, -y+1, -z$
N5–H52···O11	3.140(3)	0.97(4)	2.29(4)	146(3)	$x, y+1, z$
N5–H53···O12	2.745(3)	0.98(4)	1.77(4)	177(3)	$x-1, y+1, z$

6(c)); at H2(O2) a three-centered hydrogen bond is formed (Table 6, Figs 4(a) and 6(c)). The aggregation of two ring structures $R_2^2(4)$ and $S(6)$ can be described with a new ring $R_4^2(12)$ (Fig. 6(b)); $R_2^2(8)S(6)$ generates the new ring $R_4^2(16)$ (Fig. 6(b)). The chains $[C(8)]$ are connected by hydrogen bonds between ammonium cation and chlorine anions into a three-dimensional network (Figs. 4(a), (b) and Fig. 7(a)). Two ring skeletons $R_4^2(8)$ are built; one using the protons H52 and H53 and the other one with H51 and H52 in N^+–H···Cl^- hydrogen bonds (Fig. 7(b)). These two $R_4^2(8)$ rings aggregate into a large ring structure $R_6^3(12)$ and a ladder type chain $C(4)$ (Fig. 7(c)).

4. Concluding remarks

In the crystal structure of ammoniosalicylium chloride (**2**) the hydrogen bond N–H···Cl (including charged groups) satisfies the rigorous criterion based on the sums of van der Waals radii (H···Cl, by Pauling [11] and by Bondi [12] of 2.27 Å). The observed H···Cl distances in the structure of **2** [2.26(2), 2.29(2) and 2.30(3) Å] (Table 6) are in agreement with the values found in the crystal structures of amino acids (with charged groups) determined by neutron diffraction (2.05–2.22 Å) [13].

Different fragment definitions for search on hydrogen bond geometry of N–H···Cl type using Cambridge Structural Database [2] ended with the values clustered in the following ranges: N···Cl 3.18–3.50 Å, H···Cl 2.20–2.40 Å, ∠ N–H···Cl 157–171°, some scattering of the values below and up the limits given are also detected.

In graph-set notation the relation between the basic and complex graph sets is not defined in this paper. The strict relation is the matter of definitions which are still open for discussion.

5. Supplementary material

The H-atom coordinates and isotropic displacement parameters, and anisotropic displacement parameters for non-hydrogen atoms have been deposited with the Cambridge Crystallographic Data Centre. The data may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

Acknowledgements

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Table 6
Hydrogen bond geometry for **2**

	D···*A* (Å)	*D*–H (Å)	H···*A* (Å)	*D*–H···*A* (°)	Symm. op. on *A*
O2–H2···O12 (intra)	2.578(2)	0.83(3)	1.81(3)	154(3)	*x*, *y*, *z*
O2–H2···O2	2.811(1)	0.83(3)	2.43(3)	109(2)	$-x+2, -y, -z$
O11–H11.O12	2.683(1)	0.84(2)	1.84(2)	176(2)	$-x+1, -y-1, -z$
N5–H51···Cl	3.179(2)	0.93(2)	2.26(2)	171(2)	$x, y-1, z$
N5–H52···Cl	3.192(1)	0.91(2)	2.29(2)	171(2)	$-x+1, -y, -z+1$
N5–H53···Cl	3.202(2)	0.95(3)	2.30(3)	157(2)	*x*, *y*, *z*

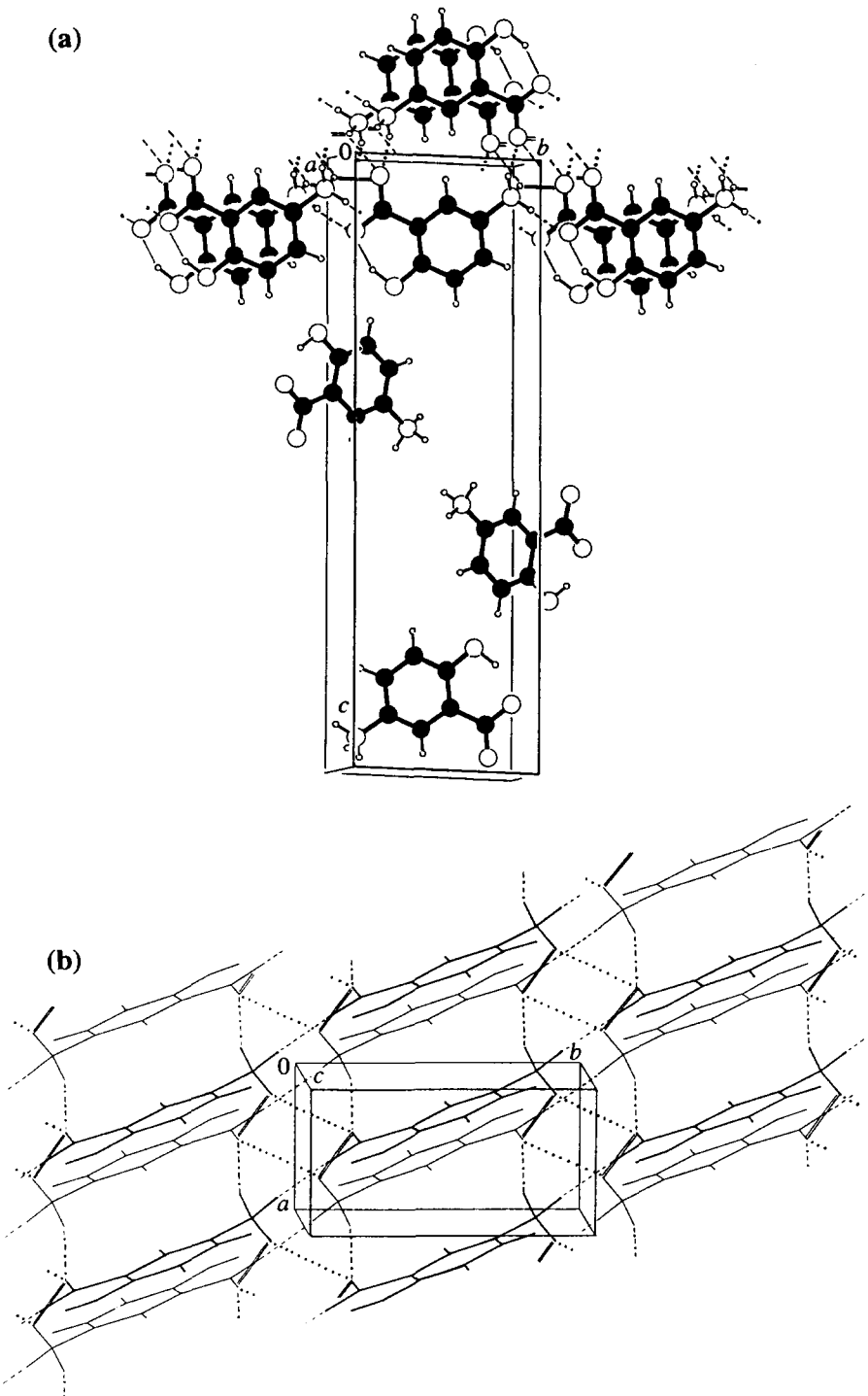

Fig. 3. Crystal packing of **1**: (a) stick and ball presentation of two-dimensional hydrogen bond pattern; (b) chicken-wire model with pronounced layered structures with hydrogen bonds in the *ab* plane. Intramolecular hydrogen bonds are omitted for clarity.

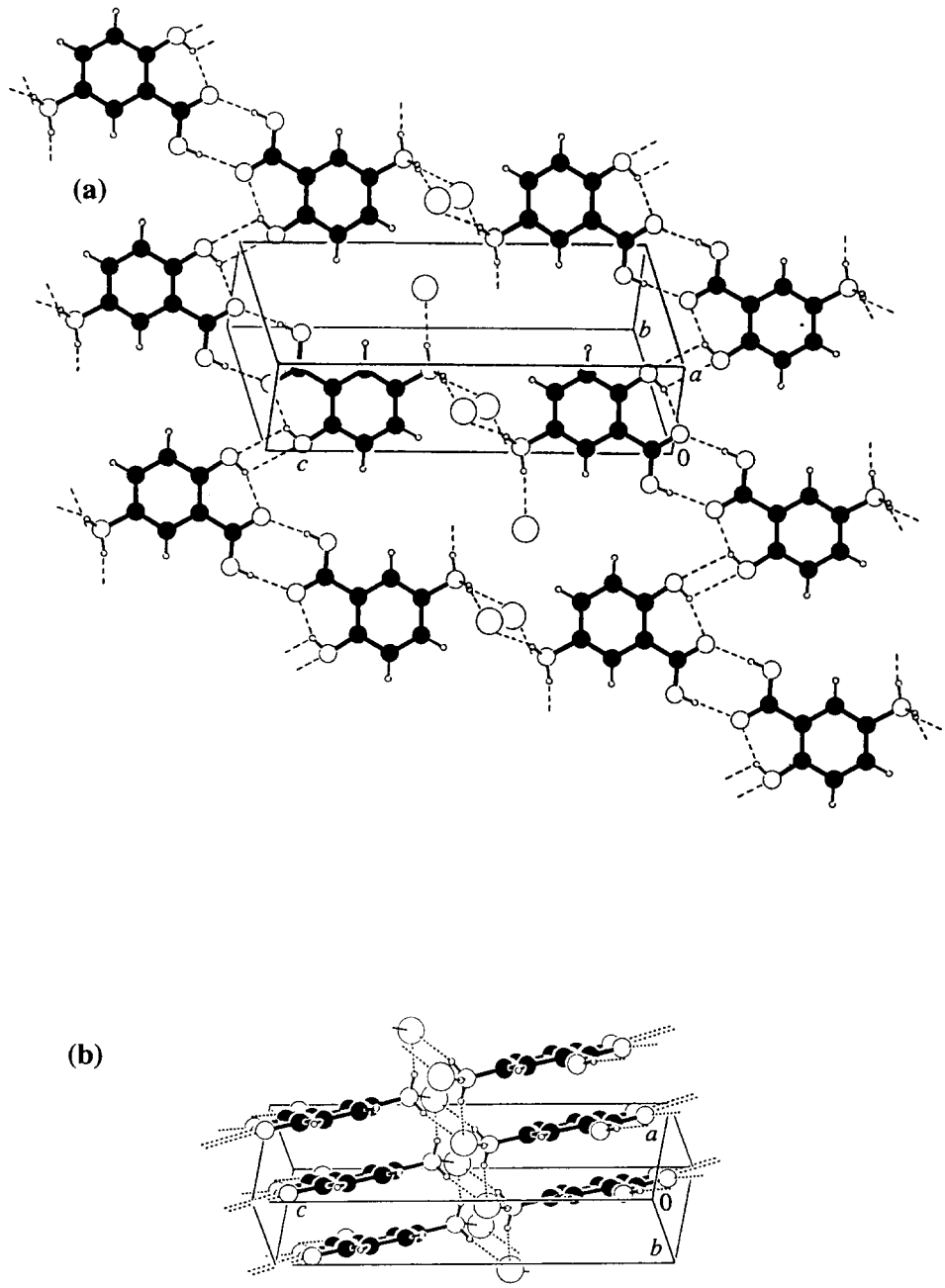

Fig. 4. Crystal packing of **2**: (a) stick and ball illustration of O–H···O hydrogen bonded chains and N^+–H···Cl^- interactions which complete a three-dimensional packing; (b) planar molecules with "head to head" orientation with highly polar regions (NH_3^+ and Cl^-).

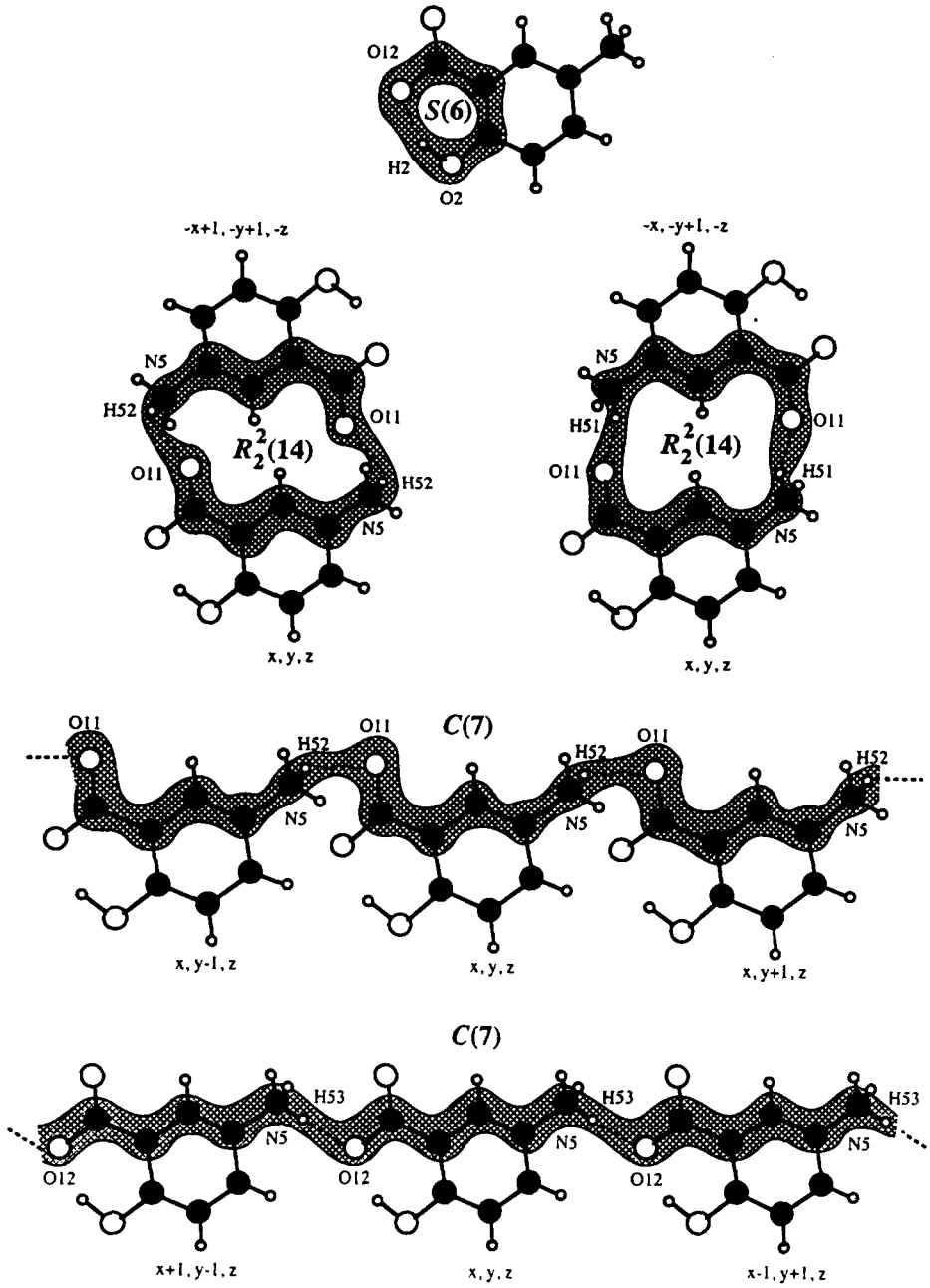

Fig. 5. Graph set assignments of hydrogen bond patterns of O–H···O(carboxylate) (intramolecular) and N^+–H···O(carboxylate) (intermolecular) types for **1**.

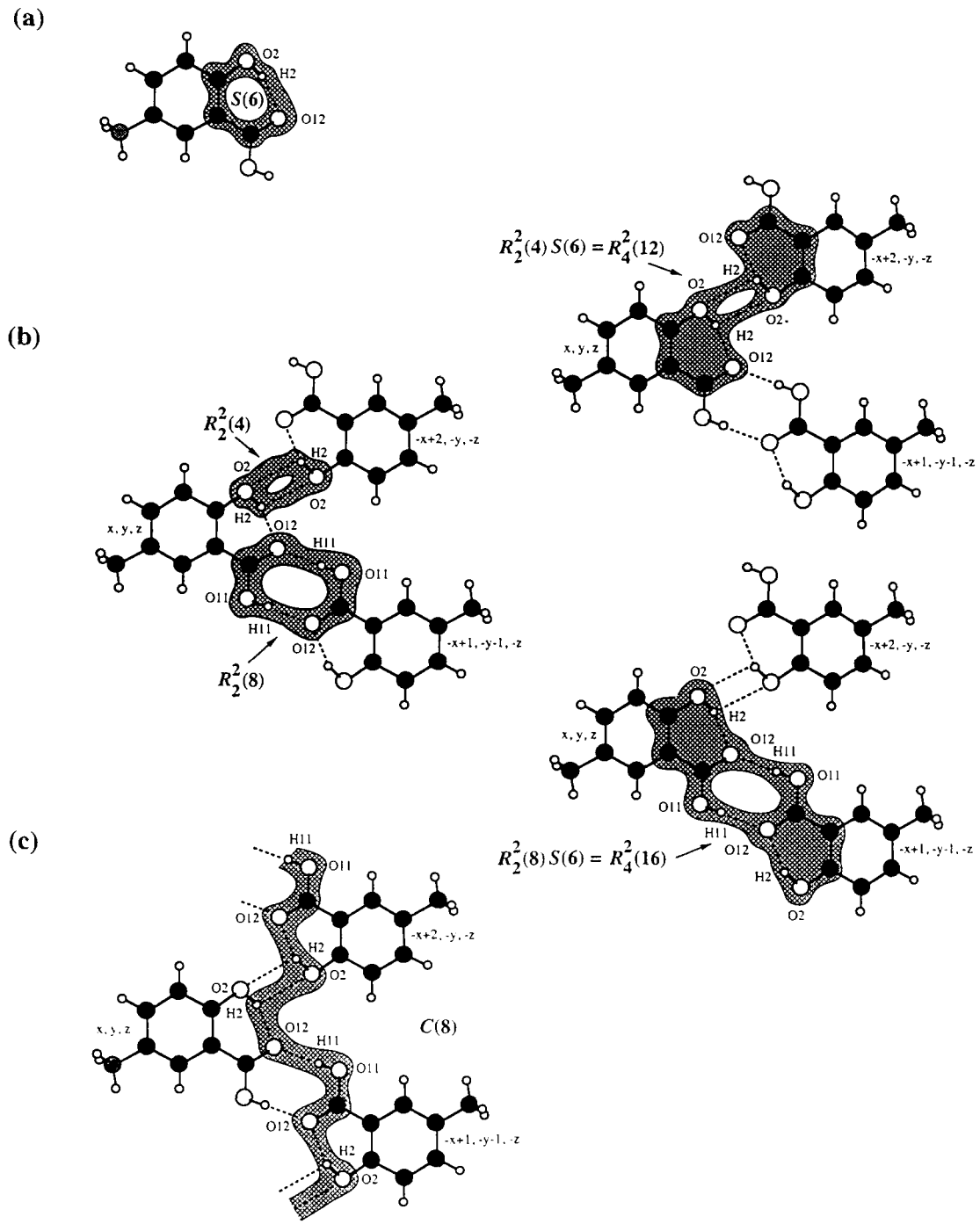

Fig. 6. Graph set assignments of hydrogen bond patterns of O–H···O type for **2**: (a) hydroxyl···carboxyl group intramolecular interaction [$S(6)$]; (b) dimers via intermolecular hydroxyl···hydroxyl [$R_2^2(4)$] and carboxyl···carboxyl group interactions [$R_2^2(8)$] and aggregation in large ring structures [$R_4^2(12)$ and $R_4^2(16)$]; (c) connection of these motifs into a chain $C(8)$.

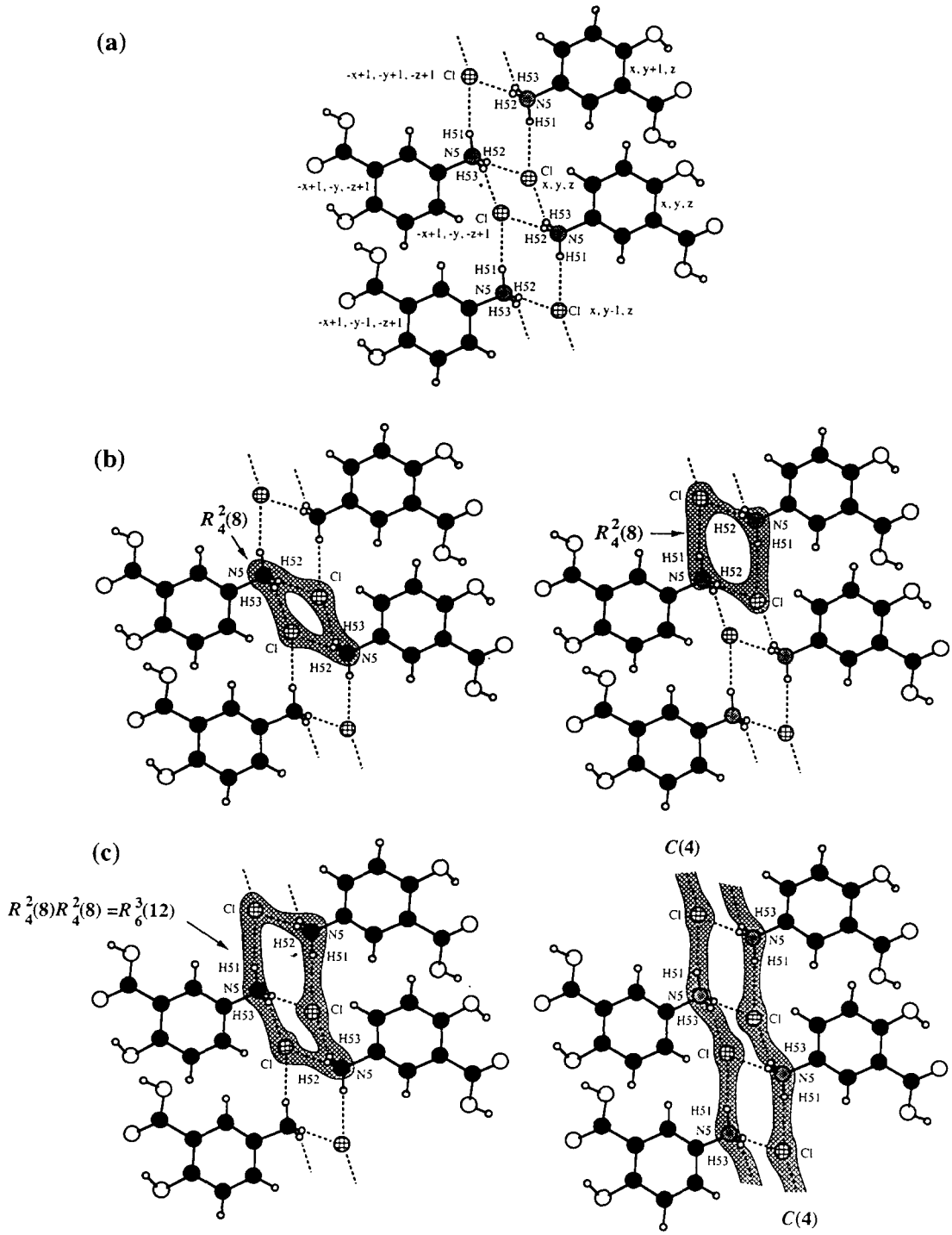

Fig. 7. Graph set assignments of hydrogen bond patterns of N^+–H···Cl^- type for **2**: (a) and (b) basic motifs; (c) aggregation into the large ring structure $R_6^3(12)$ and a chain $C(4)$.

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