Acta Cryst. (1992). C**48**, 1454–1456

Structure of Cefadroxil Monohydrate

By Whanchul Shin* and Sang Woo Cho

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, *Korea*

(*Received* 3 *July* 1991; *accepted* 13 *January* 1992)

Abstract. 7-[Amino(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate, $C_{16}H_{17}N_3O_5S.H_2O$, M_r = 381.41, orthorhombic, $P2_12_12_1$, a = 11.038 (5), b = 11.211 (6), c = 14.436 (8) Å, V = 1787 (2) Å^3, Z = 4, D_x = 1.419 g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, μ = 19.13 cm^{-1}, $F(000)$ = 800, T = 295 K, R = 0.039 for 1321 reflections with $I \geq 2\sigma(I)$. Cefadroxil exists as a zwitterion and assumes a folded conformation as in the other β-lactam compounds containing the 7β-phenylglycyl side chain. The amino atom N(18) is close to the exocyclic amide O(16) [2.718 (6) Å] but there is no intramolecular hydrogen bond. Instead, these two atoms are linked by hydrogen bonds mediated by a water molecule. There is a hydrogen bond between the phenolic O(25) and carboxyl O(12) atoms in the molecule, related by a translation along the a axis [O···H···O, 2.811 (5) Å]; H(25) is disordered between these two atoms as observed in amoxycillin trihydrate. The crystal packing consists of an intricate hydrogen-bonding network.

Introduction. Cefadroxil is one of the orally well-absorbed semisynthetic cephalosporins with a broad antibacterial spectrum against most gram-positive and gram-negative bacteria (Buck & Price, 1977). Cephalosporins usually lack oral activity but those with a 7β-arylglycine side chain have better oral activity than penicillins (Hoover, 1983). Crystal structures of penicillins containing this side chain, such as ampicillin trihydrate (James, Hall & Hodgkin, 1968), ampicillin anhydrate (Boles & Girven, 1976) and amoxycillin trihydrate (Boles, Girven & Gane, 1978) have been well elucidated. Cephaloglycine is the only cephalosporin in this class whose crystal structure has been reported, but the accuracy of its structure was very limited (R factor 20%) (Sweet & Dahl, 1970). Here we report the crystal structure of cefadroxil monohydrate.

Experimental. Pale-yellow prismatic crystals were obtained from a methanol–water solution (1:2 v/v); crystal ca 0.4 × 0.2 × 0.1 mm. A Rigaku AFC diffractometer with graphite-monochromated Cu $K\alpha$ radiation was used for data collection: $2\theta \leq 120°$; ω–2θ scan; scan speed 2° min^{-1} in 2θ; ω-scan width $(1.3 + 0.4\tan\theta)°$; background measured for 10 s on either side of the peak. Cell parameters were obtained by least-squares fit to observed 2θ values for 20 centred reflections with $25 \leq 2\theta \leq 47°$. Intensity checks for three standard reflections showed little (±1.5%) variation. 1537 independent reflections were measured (h − 12 to 0, k − 12 to 0, l 0 to 16), of which 1321 (86%) were observed with $I \geq 2\sigma(I)$ and used in the refinement. Lp corrections but no absorption or extinction corrections were applied. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1986) and refined by full-matrix least squares on F with anisotropic thermal parameters. H atoms were identified in the difference map and refined isotropically. Function $\sum w(|F_o| - |F_c|)^2$ was minimized, with $w = k/[\sigma^2(F_o) + gF_o^2]$, $\sigma(F)$ from counting statistics, k and g optimized in the least-squares procedure (k = 1.00, g = 0.00722). wR = 0.043 for 1321 observed reflections, 311 variables, R = 0.072 for all data, S = 0.644, $(\Delta/\sigma)_{max}$ = 0.398 [thermal parameter of H(18b)] in the final refinement cycle; maximum and minimum heights in final difference map 0.19 and −0.35 e Å^{-3}, respectively. All calculations were performed with *SHELX*76 (Sheldrick, 1976) on an IBM 3090 computer. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV, p. 99).

Discussion. Final atomic parameters are listed in Table 1.† An *ORTEP*II (Johnson, 1976) view of cefadroxil monohydrate with the atomic numbering scheme is presented in Fig. 1. Bond distances and angles are listed in Table 2.

Cefadroxil exists as a zwitterion with protonated amino and ionized carboxyl groups, as do the other β-lactam compounds containing the 7β-phenylglycyl

* To whom correspondence should be addressed.

† Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and dimensions involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55031 (10 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HH0558]

0108-2701/92/081454-03$06.00

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* ($Å^2 \times 10^3$)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
S(1)	2557 (1)	1868 (1)	2636 (1)	42
C(2)	2041 (5)	755 (5)	3460 (4)	40
C(3)	1007 (4)	1089 (4)	4088 (3)	30
C(4)	183 (4)	1913 (4)	3881 (3)	26
N(5)	291 (3)	2565 (3)	3048 (2)	27
C(6)	1072 (4)	2308 (4)	2259 (3)	33
C(7)	951 (4)	3656 (5)	1997 (3)	34
C(8)	262 (4)	3782 (4)	2916 (3)	36
O(9)	−119 (4)	4572 (3)	3388 (3)	62
C(10)	941 (5)	292 (6)	4937 (4)	46
C(11)	−950 (4)	2193 (4)	4423 (3)	27
O(12)	−1918 (2)	2191 (3)	3964 (2)	35
O(13)	−868 (3)	2384 (4)	5271 (2)	43
N(14)	2036 (3)	4365 (4)	1970 (3)	31
C(15)	2623 (4)	4605 (4)	1192 (3)	26
O(16)	2276 (3)	4290 (3)	424 (2)	40
C(17)	3805 (4)	5296 (4)	1318 (3)	28
N(18)	3960 (4)	6056 (4)	485 (3)	31
C(19)	4852 (4)	4455 (4)	1484 (3)	27
C(20)	5310 (5)	3709 (5)	808 (3)	42
C(21)	6250 (5)	2929 (5)	993 (4)	47
C(22)	6738 (4)	2891 (4)	1887 (3)	37
C(23)	6278 (4)	3618 (5)	2568 (3)	37
C(24)	5346 (4)	4396 (4)	2361 (3)	35
O(25)	7698 (3)	2139 (3)	2039 (3)	53
O(*w*)	2169 (5)	5539 (4)	−1235 (3)	62

Table 2. *Selected bond distances* (Å) *and angles* (°)

S(1)—C(2)	1.815 (6)	S(1)—C(6)	1.796 (5)
C(2)—C(3)	1.505 (7)	C(3)—C(4)	1.330 (6)
C(3)—C(10)	1.519 (8)	C(4)—N(5)	1.413 (5)
C(4)—C(11)	1.508 (6)	N(5)—C(6)	1.458 (5)
N(5)—C(8)	1.377 (6)	C(6)—C(7)	1.564 (7)
C(7)—C(8)	1.535 (6)	C(7)—N(14)	1.439 (6)
C(8)—O(9)	1.194 (6)	C(11)—O(12)	1.257 (5)
C(11)—O(13)	1.245 (5)	N(14)—C(15)	1.323 (6)
C(15)—O(16)	1.225 (5)	C(15)—C(17)	1.528 (6)
C(17)—N(18)	1.485 (6)	C(17)—C(19)	1.510 (6)
C(19)—C(20)	1.381 (7)	C(19)—C(24)	1.381 (6)
C(20)—C(21)	1.384 (8)	C(21)—C(22)	1.398 (7)
C(22)—C(23)	1.375 (7)	C(23)—C(24)	1.381 (7)
C(22)—O(25)	1.372 (6)		

C(3)—C(2)—S(1)	117.5 (4)	C(4)—C(3)—C(2)	123.8 (4)
N(5)—C(4)—C(3)	119.5 (4)	N(5)—C(6)—S(1)	110.9 (3)
C(6)—S(1)—C(2)	95.8 (2)	C(6)—N(5)—C(4)	127.8 (3)
C(7)—C(6)—S(1)	114.7 (3)	C(7)—C(6)—N(5)	86.9 (3)
C(7)—C(8)—N(5)	91.0 (3)	C(8)—N(5)—C(4)	129.0 (3)
C(8)—N(5)—C(6)	95.8 (3)	C(8)—C(7)—C(6)	85.6 (3)
O(9)—C(8)—N(5)	131.6 (4)	O(9)—C(8)—C(7)	137.3 (5)
C(10)—C(3)—C(2)	112.1 (4)	C(10)—C(3)—C(4)	123.8 (4)
C(11)—C(4)—C(3)	126.5 (4)	C(11)—C(4)—N(5)	113.8 (4)
O(12)—C(11)—C(4)	115.5 (4)	O(13)—C(11)—C(4)	119.0 (4)
O(13)—C(11)—O(12)	125.5 (4)	N(14)—C(7)—C(6)	118.0 (4)
N(14)—C(7)—C(8)	112.7 (4)	C(15)—N(14)—C(7)	122.9 (4)
O(16)—C(15)—N(14)	123.8 (4)	C(17)—C(15)—N(14)	114.8 (4)
C(17)—C(15)—O(16)	121.4 (4)	N(18)—C(17)—C(15)	107.0 (4)
C(19)—C(17)—C(15)	110.9 (4)	C(19)—C(17)—N(18)	113.4 (4)
C(20)—C(19)—C(17)	123.1 (4)	C(21)—C(20)—C(19)	121.4 (4)
C(22)—C(21)—C(20)	119.1 (5)	C(23)—C(22)—C(21)	120.0 (4)
C(23)—C(24)—C(19)	121.6 (4)	C(24)—C(19)—C(17)	118.5 (4)
C(24)—C(19)—C(20)	118.3 (4)	C(24)—C(23)—C(22)	119.6 (4)
O(25)—C(22)—C(21)	117.7 (4)	O(25)—C(22)—C(23)	122.3 (4)

Table 3. *Hydrogen-bond geometry* (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N(14)—H···O(*w*^{i})	0.78 (6)	2.00 (6)	2.738 (6)	156 (6)
N(18)—H(*a*)···O(9^{ii})	1.13 (8)	2.39 (8)	3.361 (6)	143 (6)
N(18)—H(*a*)···O(*w*)	1.13 (8)	2.49 (8)	3.226 (7)	122 (5)
N(18)—H(*b*)···O(12^{iii})	0.79 (5)	2.03 (6)	2.708 (5)	143 (6)
N(18)—H(*c*)···O(13^{ii})	0.80 (6)	1.98 (6)	2.755 (5)	164 (6)
O(25)—H···O(12^{iv})	1.5 (2)	1.4 (2)	2.811 (5)	152 (2)
O(*w*)—H(*a*)···O(13^{iii})	1.03 (6)	1.94 (6)	2.877 (6)	150 (5)
O(*w*)—H(*b*)···O(16)	0.78 (7)	2.03 (7)	2.777 (5)	162 (7)

Symmetry code: (none) x, y, z; (i) $0.5 - x, 1 - y, 0.5 + z$; (ii) $0.5 - x, 1 - y, -0.5 + z$; (iii) $-x, 0.5 + y, 0.5 - z$; (iv) $1 + x, y, z$.

side chain, such as ampicillin, amoxycillin and cephaloglycine. Molecular dimensions of the cephem nucleus agree well with those of the other 3-cephem derivatives [see, for example, Domiano, Nardelli, Balsamo, Macchia, Macchia & Meinardi (1978)]. The cefadroxil molecule assumes a folded conformation typically observed in the β-lactam compounds containing the same side chain. In this conformation the 3-cephem nucleus and the phenyl ring are on the same side of the exocyclic amide plane. The C(6)—N(14)—C(15)—C(17), N(14)—C(15)—C(17)—C(19) and C(15)—C(17)—C(19)—C(20) torsion angles are 98.1 (6), 87.6 (5) and 69.5 (5)° in cefadroxil, 141.9, 98.8 and 60.9° in ampicillin anhydrate, 133.8, 86.9 and 76.3° in amoxycillin trihydrate (also in nearly isomorphous ampicillin trihydrate), and 123, 74 and 36° in cephaloglycine, respectively. There is a certain degree of flexibility in the relative orientation

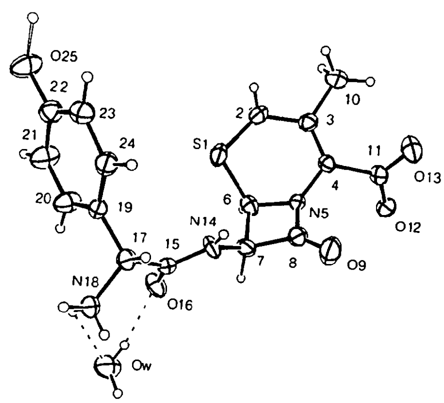

Fig. 1. *ORTEP*II (Johnson, 1976) drawing of cefadroxil monohydrate with atomic numbering scheme. Thermal ellipsoids are drawn at the 50% probability level. The dotted line denotes the hydrogen bond.

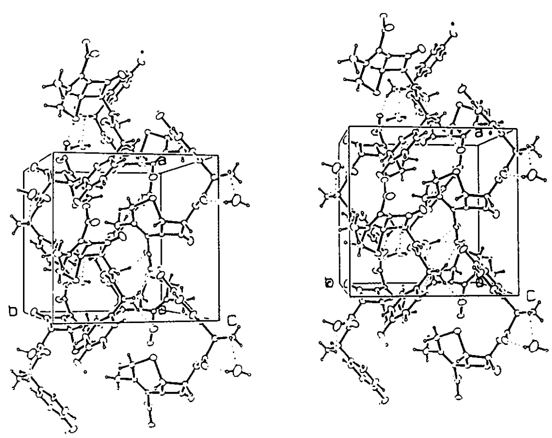

Fig. 2. Stereoscopic *ORTEP*II (Johnson, 1976) packing drawing of cefadroxil monohydrate. The dotted line denotes the hydrogen bond.

between the 3-cephem nucleus and the exocyclic amide group. However, the orientation of the 7β-phenylglycyl group with respect to the amide group is nearly constant in ampicillin, amoxycillin and cefadroxil despite different crystal-packing environments.

Although formation of the intramolecular N(18)—H···O(16) hydrogen bond has been suggested based on the poorly determined crystal structure of cephaloglycine (Sweet & Dahl, 1970), such a direct hydrogen bond has not been observed in any β-lactam compounds containing the 7β-phenylglycyl side chain. In cefadroxil, the amino N(18) atom is close to the exocyclic amide O(16) [N···O = 2.718 (6) Å, O(16)—C(15)—C(17)—N(18) = 33.0 (4)°] but there is no intramolecular hydrogen bond. Instead, these two atoms are linked by hydrogen bonds mediated by a water molecule, although the N(18)—H(*a*)···O(*w*) hydrogen bond is very weak (see Table 3). In amoxycillin trihydrate and ampicillin trihydrate, N(14), instead of N(18), and O(16) are linked by hydrogen bonds also mediated by a water molecule. There is no intramolecular hydrogen-bonding interaction between N(18) and O(16), even in ampicillin anhydrate.

The crystal packing (Fig. 2) consists of an intricate hydrogen-bonding network. H(18*a*) of the protonated amino group is involved in a very weak three-centred hydrogen bond with O(*w*) and β-lactam keto O(9). The remaining two H atoms on N(18) are hydrogen-bonded to the carboxyl O(12) and O(13) atoms in the two molecules related by a twofold screw-axis symmetry along the *c* axis. Each carboxyl O atom accepts two hydrogen bonds. There is a hydrogen bond between the phenolic O(25) and carboxyl O(12) atoms in the molecule, related by a translation along the *a* axis [O···H···O = 2.811 (5) Å]; H(25) is disordered between these two O atoms. The same phenomenon has been observed in amoxycillin trihydrate. Each water molecule is involved in four hydrogen bonds in a tetrahedral configuration.

We are grateful to the Korea Science and Engineering Foundation for support of this research.

References

BOLES, M. O. & GIRVEN, R. J. (1976). *Acta Cryst.* **B32**, 2279–2284.
BOLES, M. O., GIRVEN, R. J. & GANE, P. A. C. (1978). *Acta Cryst.* **B34**, 461–466.
BUCK, R. E. & PRICE, K. E. (1977). *Antimicrob. Agents Chemother.* **11**, 324–330.
DOMIANO, P., NARDELLI, M., BALSAMO, A., MACCHIA, B., MACCHIA, F. & MEINARDI, G. (1978). *J. Chem. Soc. Perkin Trans.* 2, pp. 1082–1087.
HOOVER, J. R. E. (1983). *Antibiotics Containing the β-Lactam Structure*, Vol. II, edited by A. L. DEMAIN & N. A. SOLOMON, pp. 119–245. Berlin: Springer-Verlag.
JAMES, M. N. G., HALL, D. & HODGKIN, D. C. (1968). *Nature (London)*, **220**, 168–170.
JOHNSON, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.
SHELDRICK, G. M. (1986). *SHELXS86*. Program for the solution of crystal structures. Univ. of Göttingen, Germany.
SWEET, R. M. & DAHL, L. F. (1970). *J. Am. Chem. Soc.* **92**, 5489–5507.

Acta Cryst. (1992). **C48**, 1456–1458

Structure of 3,4-Dimethyl-5-methylamino-1,2,4-thiadiazolium Chloride Monohydrate

BY FEN-LING LIAO AND SUE-LEIN WANG*

Department of Chemistry, National Tsing-Hua University, Hsinchu 30043, *Taiwan*

AND LONG-LI LAI AND DAVID H. REID

Centre for Molecular Design, Department of Chemistry, University of the Witwatersrand, Wits 2050, *Johannesburg, South Africa*

(*Received* 7 *August* 1991; *accepted* 7 *January* 1992)

Abstract. $C_5H_{10}N_3S^+.Cl^-.H_2O$, $M_r = 197.69$, monoclinic, $P2_1/n$, $a = 5.600$ (1), $b = 10.833$ (2), $c = 15.281$ (2) Å, $\beta = 97.22$ (1)°, $V = 919.7$ (3) Å^3, $Z = 4$, $D_x = 1.428$ Mg m^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.585$ mm^{-1}, $F(000) = 416$, $T = 297$ K, final $R = 0.0454$ for 1635 independent reflections [$1364 > 3\sigma(I)$]. The methyl substituent of the 5-methylamino group lies in an *E* orientation with respect to the methyl group on N(4).

Introduction. The determination of the structure of the title compound (6) arose from work on the

* To whom correspondence should be addressed.

0108-2701/92/081456-03$06.00