Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Clarithromycin hydrochloride 3.5-hydrate

Masood Parvez *et al.*

Electronic paper
This paper is published electronically. It meets the data-validation criteria for publication in Acta Crystallographica Section C. The submission has been checked by a Section C Co-editor though the text in the 'Comments' section is the responsibility of the authors.

© 2000 International Union of Crystallography • Printed in Great Britain – all rights reserved

Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Clarithromycin hydrochloride 3.5-hydrate

Masood Parvez,[a]* M. Saeed Arayne,[b] Rizwana Sabri[c] and Najma Sultana[c]

[a]Department of Chemistry, The University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada T2N 1N4, [b]Department of Chemistry, University of Karachi, Karachi 75270, Pakistan, and [c]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Karachi 75270, Pakistan
Correspondence e-mail: parvez@ucalgary.ca

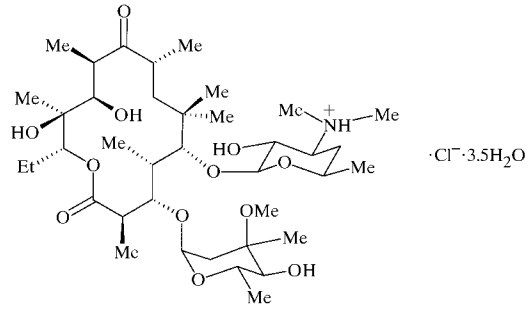
Received 27 June 2000
Accepted 13 July 2000

Data validation number: IUC0000194

The absolute configuration was determined for the title compound, $C_{38}H_{70}NO_{13}^{+}\cdot Cl^{-}\cdot 3.5H_2O$. The cation contains a 14-membered macrocyclic lactone and two sugars, namely cladinose and desosamine. The six-membered rings of the sugars adopt chair conformations. The structure is stabilized by strong hydrogen bonds, with O···O distances in the range 2.486 (9)–2.830 (5) Å; other distances are N···O = 2.860 (5), N···Cl = 3.134 (4) and O···Cl = 3.303 (4) Å.

Comment

Clarithromycin (6-*O*-methylerythromycin) is an antibiotic widely used in the treatment of acute sinusitis (Clifford *et al.*, 1999), toxoplasmosis, encephalitis (Saba *et al.*, 1993), diarrhea due to cryptosporidium (Rehg, 1991), and *H. pyloria* infection associated with peptic ulcer (Al-Assi *et al.*, 1994). Drug interactions of clarithromycin are circumstantial to its oral absorption as well as with the concomitant use of other drugs (Hassan *et al.*, 1999). A number of drug interactions of clarithromycin with several drugs have been reported (Cederbrant *et al.*, 1994; Hill *et al.*, 1996). There have been no clarithromycin–metal interactions reported in the literature although the interactions of erythromycin with antacids containing di- and trivalent metal cations have been reported (Arayne & Sultana, 1993). Our attempts to prepare Mg and Mn complexes of clarithromycin, using metal chlorides, in ethylacetate, lead to the formation of clarithromycin hydrochloride 3.5-hydrate, (I). In this article, we report the absolute structure of (I). The asymmetric unit of (I) contains clarithromycin hydrochloride and 3.5 water molecules of solvation. The clarithromycinium cation is composed of a 14-membered macrocyclic lactone, aglycone, wherein the asymmetric centers have 2*R*, 3*S*, 4*R*, 5*R*, 6*R*, 8*R*, 10*R*, 11*R*, 12*S* and 13*R* configurations, which are the same as those established for erythromycin A (Harris *et al.*, 1965) with the exception of the configuration at C4 which is 4*S* in the latter. The same relative configurations of these centers have been observed in the structure of clarithromycin methanol solvate (Iwasaki *et al.*, 1993), although the authors have assigned the 4*S* configuration in this case. The absolute configuration of the sugar moieties, namely cladinose and desosamine, attached at C3 and C5, respectively, agree with the previously established configurations of these sugars (Lemal *et al.*, 1962; Richardson, 1963)



(I)

with the asymmetric centers being 17*R*, 19*R*, 20*S*, 21*S*, 26*S*, 27*R*, 28*S* and 30*R* in (I). The carbonyl groups, the hydroxyl groups and the methoxyl group attached to the macrocyclic ring lie on the same side of the ring forming a hydrophilic region.

The bond distances and angles in (I) are in excellent agreement with the corresponding dimensions reported for the structures of similar antibiotics, *e.g.* erythromycin·HI·2H_2O (Harris *et al.*, 1965), 11-4″-bis[*O*-(*p*-bromobenzoyl)]oleandomycin (Ogura *et al.*, 1978), 23672RP – a macrolide antibiotic (Arnoux *et al.*, 1980), the Zn complex of erythromycin A (Oliver & Strickland, 1986), clarithromycin methanol solvate (Iwasaki *et al.*, 1993), and erythromycin A, erythromycin B and clarithromycin (Stephenson *et al.*, 1997). The mean vaules of the bond distances in (I) are: Csp^3-Csp^3 1.524 (16), Csp^3-Csp^2 1.512 (4), $N-Csp^3$ 1.503 (16), $O-Csp^3$ 1.426 (16) and C═O 1.202 (18) Å; the $O-Csp^2$ bond is 1.348 (5) Å.

The six-membered rings of the sugars cladinose and desosamine in (I) adopt chair conformations with puckering parameters (Cremer & Pople, 1975): Q = 0.521 (5) and 0.578 (5) Å, θ = 170.0 (6) and 3.6 (5)°, and φ = 62 (3) and 304 (8)°.

The structure is stabilized by extensive hydrogen bonding, with O···O distances in the range 2.486 (9)–2.830 (5) Å; other distances are N···O = 2.860 (5), N···Cl = 3.134 (4) and O···Cl = 3.303 (4) Å (Table 2).

Experimental

Clarithromycin (0.5×10^{-3} moles) was dissolved in ethyl acetate (20 ml) and mixed with metal chloride ($MgCl_2/MnCl_2$, 1.0×10^{-3} moles) solution in ethyl acetate (10–15 ml) and a few drops of water. The solution was refluxed for 3 h. Colorless crystals formed over a period of 2–3 weeks.

Crystal data

$C_{38}H_{70}NO_{13}^{+}\cdot Cl^{-}\cdot 3.5H_2O$
M_r = 847.46
Orthorhombic, $P2_12_12_1$
a = 14.409 (2) Å
b = 16.489 (3) Å
c = 19.267 (3) Å
V = 4577.6 (13) Å^3
Z = 4
D_x = 1.228 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 20.0–30.0°
μ = 1.30 mm^{-1}
T = 293 (2) K
Block, colorless
0.50 × 0.38 × 0.35 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: empirical ψ scan (3 reflections; North *et al.*, 1968)
T_{min} = 0.56, T_{max} = 0.66
8735 measured reflections
8291 independent reflections
5541 reflections with $I > 2\sigma(I)$
R_{int} = 0.062
θ_{max} = 68.°
$h = 0 \rightarrow 17$
$k = 0 \rightarrow 19$
$l = -23 \rightarrow 23$
3 standard reflections
every 200 reflections
intensity decay: 12.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.150
S = 1.05
8291 reflections
532 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.047P)^2 + 3.56P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = −0.01 (3)

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.348 (5)	O8—C26	1.407 (5)
O1—C13	1.458 (5)	O8—C30	1.437 (5)
O2—C1	1.184 (5)	O9—C27	1.421 (5)
O3—C17	1.416 (5)	O10—C35	1.400 (6)
O3—C3	1.438 (5)	O10—C6	1.434 (5)
O4—C17	1.410 (5)	O11—C9	1.220 (5)
O4—C21	1.448 (5)	O12—C11	1.431 (5)
O5—C23	1.426 (5)	O13—C12	1.424 (5)
O5—C19	1.431 (5)	N1—C31	1.490 (6)
O6—C20	1.422 (5)	N1—C32	1.493 (6)
O7—C26	1.396 (5)	N1—C28	1.525 (5)
O7—C5	1.446 (5)		
C1—O1—C13	118.9 (3)	C26—O8—C30	112.0 (3)
C17—O3—C3	115.2 (3)	C35—O10—C6	120.4 (4)
C17—O4—C21	116.3 (3)	C31—N1—C32	110.5 (4)
C23—O5—C19	116.2 (4)	C31—N1—C28	114.9 (4)
C26—O7—C5	116.6 (3)	C32—N1—C28	111.6 (4)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O6—H6···O13^{i}	0.82	1.86	2.660 (4)	164
O13—H13···O16^{ii}	0.82	2.05	2.767 (5)	146
O9—H9···O17	0.82	2.03	2.486 (9)	114
O13—H13···O12	0.82	2.27	2.683 (5)	111
O12—H12···O11	0.82	2.14	2.830 (5)	142
O9—H9···Cl1	0.82	2.61	3.303 (4)	143
N1—H1···O9	0.91	2.40	2.860 (5)	112
N1—H1···Cl1	0.91	2.29	3.134 (4)	154

Symmetry codes: (i) $x-1, y, z$; (ii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$.

In the lattice, there were three molecules of water of solvation with full and one with partial occupancy. Most of the H atoms and specifically the hydroxyl H atoms were located from difference maps and all H atoms were placed at geometrically idealized positions (O—H 0.82, N—H 0.91 and C—H 0.96–0.98 Å) utilizing a riding model, and a torsional parameter was refined for each methyl group. Water H atoms were ignored. Friedel pairs (3666) were collected and were not merged. The Flack (1983) parameter for the inverted structure was 1.01 (3).

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1994); program(s) used to solve structure: *SAPI*91 (Fan, 1991); program(s) used to refine structure: *SHELXTL*97 (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL*97.

References

Al-Assi, M. T., Ramirez, F. C., Lew, G. M., Genta, R. M. & Graham, D. Y. (1994). *Am. J. Gastroenterol.* **89**, 1203–1025.
Arayne, M. S. & Sultana, N. (1993). *Pharmazie*, **48**, 599–602.
Arnoux, B., Pascard, C., Raynaud, L. & Lunel, J. (1980). *J. Am. Chem. Soc.* **102**, 3605–3608.
Cederbrant, G. K., Kahlmeter, G., Schalen, C. & Kamme, C. (1994). *J. Antimicrob. Chemother.* **34**, 1025–1029.
Clifford, K., Huck, W., Shan, M., Tosiello, R., Echols, R. M. & Heyd, A. (1999). *Ann. Otol. Rhinol. Laryngol.* **108**, 360–367.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Enraf–Nonius (1989). *CAD*-4 *Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.
Fan, H.-F. (1991). *SAPI*91. Rigaku Corporation, Tokyo, Japan.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Harris, D. R., McGeachin, S. G. & Mills, H. H. (1965). *Tetrahedron Lett.* pp. 679–685.
Hassan, I. J., Stark, R. M., Greenman, J. & Millar, M. R. (1999). *Antimicrob. Agents Chemother.* **43**, 1387–1392.
Hill, D. R., Celebuski, J. E., Pariza, R. J., Chorghade, M. S., Levenberg, M., Pagano, T., Cleary, G., West, P. & Whittern, D. (1996). *Tetrahedron Lett.* **37**, 787–790.
Iwasaki, H., Sugawara, Y., Adachi, T., Morimoto, S. & Watanabe, Y. (1993). *Acta Cryst.* C**49**, 1227–1230.
Lemal, D. M., Pacht, P. D. & Woodward, R. B. (1962). *Tetrahedron.* **18**, 1275–1293.
Molecular Structure Corporation (1994). *TEXSAN*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Ogura, H., Furuhata, K., Harada, Y. & Iitaka, Y. (1978). *J. Am. Chem. Soc.* **100**, 6733–6737.
Oliver, J. D. & Strickland, L. C. (1986). *Acta Cryst.* C**42**, 952–956.
Rehg, J. E. (1991). *J. Infect. Dis.* **163**, 1293–1296.
Richardson, A. C. (1963). *Proc. Chem. Soc.* p. 131.
Saba, J., Morlat, P., Raffi, F., Hazebroucq, V., Leport, C. & Vilde, J. L. (1993). *Eur. J. Clin. Microbiol. Infect. Dis.* **12**, 853–856.
Sheldrick, G. M. (1997). *SHELXTL*97. Version 5.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Stephenson, G. A., Stowell, J. G., Toma, P. H., Pfeiffer, R. R. & Byrn, S. R. (1997). *J. Pharm. Sci.* **86**, 1239–1244.