Data collection

Enraf–Nonius CAD-4-MachS diffractometer
$\omega/2\theta$ scans
Absorption correction: Gaussian by integration (Sheldrick, 1976)
T_{min} = 0.041, T_{max} = 0.166
4197 measured reflections
3332 independent reflections
2462 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 27.47°
$h = -1 \rightarrow 8$
$k = -12 \rightarrow 12$
$l = -16 \rightarrow 16$
3 standard reflections
frequency: 160 min
intensity decay: 18%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.119
S = 1.055
3332 reflections
208 parameters
Methine H atoms refined, others riding
$w = 1/[\sigma^2(F_o^2) + (0.0563P)^2 + 1.0706P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.790 e Å^{-3}
$\Delta\rho_{min}$ = −0.667 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.0116 (15)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Br1—C1	1.927 (5)	C2—C3	1.541 (6)
Br2—C4	1.952 (5)	C3—C4	1.522 (6)
Br3—C4	1.921 (5)	C4—C5	1.529 (6)
C1—C2	1.545 (6)	C7—C10	1.551 (7)
C1—C10	1.557 (6)	C8—C9	1.308 (9)
C9—C1—C2	109.2 (4)	C3—C4—C5	105.4 (3)
C9—C1—C10	99.8 (4)	C3—C4—Br3	112.7 (3)
C2—C1—C10	100.7 (3)	C5—C4—Br3	112.9 (3)
C9—C1—Br1	115.8 (4)	C3—C4—Br2	113.1 (3)
C2—C1—Br1	113.5 (3)	C5—C4—Br2	104.0 (3)
C10—C1—Br1	116.0 (3)	Br3—C4—Br2	108.5 (2)
C13—C3—C4	116.8 (4)	C7—C10—C1	92.1 (3)
C13—C3—C2	115.0 (4)		

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *CAD-4 Software*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: TA1187). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). C**53**, 1917–1919

Spirapril Hydrochloride Hydrate

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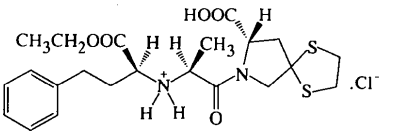
(Received 30 April 1996; accepted 3 June 1997)

Abstract

The crystal structure of the monohydrate form of spirapril hydrochloride, (8*S*-{7[*R**(*R**)],8*R**})-7-(2-{[1-(ethoxycarbonyl)-3-phenylpropyl]amino}-1-oxopropyl)-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid hydrochloride, $C_{22}H_{31}N_2O_5S_2^+.Cl^-.H_2O$, was determined. The spirapril molecules adopt a *trans* conformation along the amide bond. The incorporated water molecules form hydrogen bonds with the host molecules.

Comment

Spirapril hydrochloride, (I), belongs to a class of *N*-carboxyalkyl dipeptide ACE inhibitors. Like many other of these dipeptide drugs, it is not very stable in the solid state. The major degradation pathway involves an intramolecular cyclization reaction (Strickley, Visor, Lin & Gu, 1989; Gu, Strickley, Chi & Chowhan, 1990). In our study of the chemical stability of pharmaceutical solids, we chose spirapril hydrochloride as a model compound to investigate the effect of molecular mobility on solid-state reactivity. The structure of spirapril hydrochloride monohydrate was determined and the information on the molecular geometry will aid in the understanding of the molecular details of the cyclization reaction.



(I)

An *ORTEP*II (Johnson, 1976) drawing of spirapril hydrochloride is presented in Fig. 1. For the sake of simplicity, the protonated spirapril moiety is referred to as the cation. It adopts a *trans* conformation at the amide bond since C5 and C8 (higher priority than C11) are on the opposite side of the amide bond and the torsion angle between C8—N7 and C6—C5 is −175.7 (3)°. The same kind of *trans* conformation is also observed in other *N*-carboxyalkyl dipeptide ACE inhibitors such as quinapril hydrochloride (Hausin & Codding, 1991) and enalapril maleate (Precigoux, Geoffre & Leroy,

1986). For spirapril hydrochloride, the two functional groups that are involved in the cyclization reaction, the amino group and the carboxylic acid group, are not in the proper orientation to cyclize because the amino N4 atom and the carbonyl C81 atom are separated by a distance of 5.272 (4) Å. A certain degree of conformational mobility along C5—C6—N7 would be required for the reaction to take place in the crystalline state. Molecular modeling on the rotational energy barrier along C5—C6 and C6—N7 would be necessary to examine the effect of molecular conformation on this solid-state intramolecular reaction. In addition to the *trans* conformation, the extended conformation of the phenylpropyl group [a torsion angle of −174.5 (4)° for spirapril C3—C2—C1—C21] is also observed in quinapril and enalapril. The methyl group of the ester group in the spirapril cation is disordered and it occupies one of the two positions with different probabilities. The occupancy factors for C20*A* and C20*B* are 0.659 (8) and 0.341 (8), respectively.

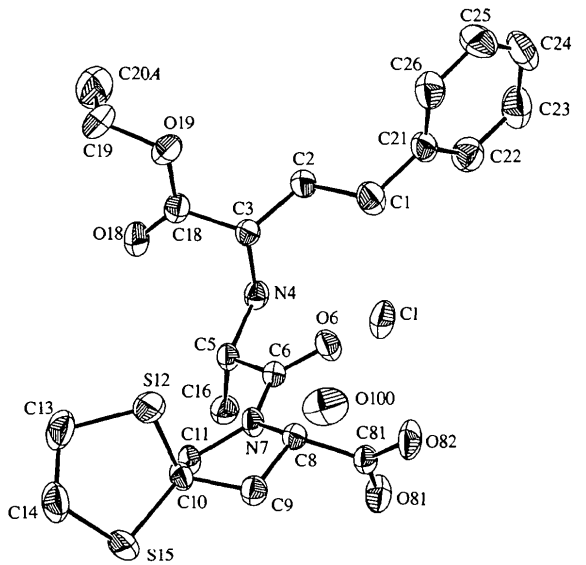


Fig. 1. *ORTEP*II (Johnson, 1976) diagram of spirapril hydrochloride with the ester group in a *trans* conformation. The ellipsoids are plotted at the 50% probability level.

The unit cell generated by *QUANTA*4.0 (Molecular Simulations Incorporated, 1994) is shown in Fig. 2. Water molecules sit in tunnels parallel to the *b* axis. The chlorine anion, cation and water molecule form hydrogen bonds with each other (Fig. 3). The hydrogen-bond data are listed in Table 1. Both the carbonyl O81 atom and the hydroxyl group O82—H82 of the carboxyl group participate in hydrogen bonding. The hydroxyl group is hydrogen bonded to the chlorine anion and the carbonyl O atom is hydrogen bonded to the amine H4*B* atom of an adjacent molecule. The two cations are further connected by a third hydrogen bond between the chlorine anion and the second H atom, H4*A*, of the

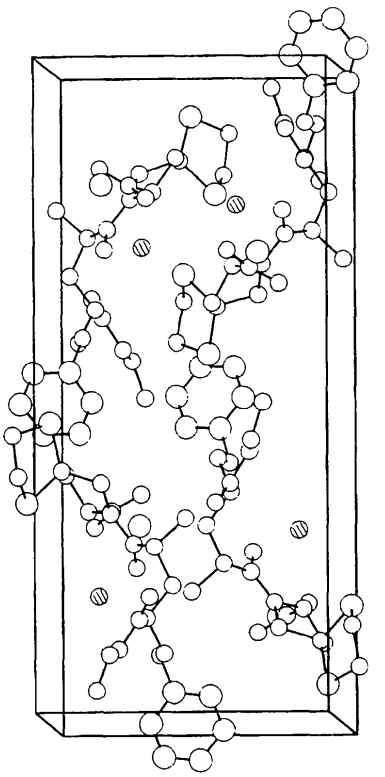


Fig. 2. Unit cell viewed down the *b* axis. Water O atoms are shaded.

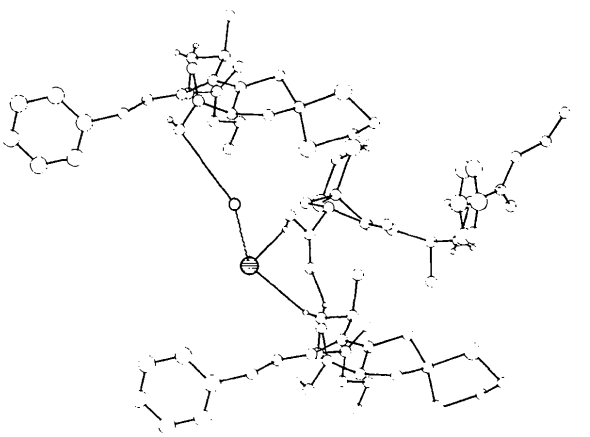


Fig. 3. Hydrogen-bonding scheme. The dark circle represents the O atom of the water molecule. The shaded dark circle represents the chlorine anion. Hydrogen bonds are drawn as dotted lines.

protonated amine group. The water molecule forms one hydrogen bond with the chlorine anion and a second hydrogen bond with the hydroxyl O82 atom in the cation.

Experimental

Spirapril hydrochloride was a gift from Sandoz Research Institute, East Hanover, NJ, USA. The monohydrate form was prepared by slow evaporation from wet methanol.

Crystal data

$C_{22}H_{31}N_2O_5S_2^+.Cl^-.H_2O$
M_r = 521.10
Orthorhombic
$P2_12_12_1$
a = 10.5075 (15) Å
b = 10.6251 (15) Å
c = 23.407 (3) Å
V = 2613.1 (6) Å^3
Z = 4
D_x = 1.325 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 20–24°
μ = 0.34 mm^{-1}
T = 296 K
Needle
0.63 × 0.38 × 0.32 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
$3\theta/5\theta$ scans
Absorption correction: none
3482 measured reflections
3482 independent reflections
2786 reflections with $I > 2\sigma(I)$

θ_{max} = 27.82°
$h = -13 \rightarrow 13$
$k = 0 \rightarrow 13$
$l = 0 \rightarrow 30$
3 standard reflections
frequency: 83 min
intensity decay: 0.16%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.108
S = 1.09
3482 reflections
422 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0461P)^2 + 0.7969P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.017

$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = −0.22 (10)

Table 1. *Hydrogen-bonding data (Å)*

O82···Cl^i	2.990 (3)	O100···O82	3.315 (5)
N4···Cl	3.212 (3)	O100···Cl^{iii}	3.326 (5)
N4···O81^{ii}	2.866 (4)		

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

H atoms, except for those in the ethoxy group, are refined isotropically. H19*A* and H19*B* are calculated based on C20*A*. Torsion angles as well as the occupancy factor for C20*A* and C20*B* were refined. The average bond length and the bond angles are in agreement with the accepted values. The absolute configuration of the molecule was chosen based on previous studies.

Data collection: *CAD-4 Operations Manual* (Enraf–Nonius, 1977). Cell refinement: *CAD-4 Operations Manual*. Data reduction: *PROCESS* in *MolEN* (Fair, 1990). Program(s) used to solve structure: *SIR* (Altomare *et al.*, 1994) (direct methods). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *CIF VAX* in *MolEN*.

We would like to thank Dr Phillip Fanwick for his assistance with the refinement of this structure. This work is supported by the Purdue/Wisconsin Program on the Effect of Water on Molecular Mobility of Crystalline and Amorphous Solids.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1260). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). C**53**, 1919–1921

Methyl 1-Benzyl-3-cyclohexyl-2-oxopyrrolidine-2-carboxylate

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(Reçu le 9 avril 1997, accepté le 17 juillet 1997)

Abstract

In the crystal structure of the title compound, $C_{19}H_{25}NO_3$, the γ-lactam heterocyclic ring is planar. The cyclohexyl and methoxycarbonyl substituents are *trans*.

Commentaire

La structure de α-cyclohexyl-β-methoxycarbonyl-γ-lactame, (I), a été établie par diffraction des rayons X sur monocristal afin de déterminer la configuration de la molécule et surtout la disposition des deux atomes