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The Crystal and Molecular Structures of Ceftizoxime and Ceftizoxime Monohydrochloride Monohydrate

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The crystal and molecular structures of ceftizoxime (CZX) and its monohydrochloride monohydrate (CZX-HCl) were elucidated by X-ray structure analysis. The aminothiazolyl-methoxyimino group in the cephem C(7) substituent of both substances is in a quasi coplane, as in other cephalosporins with this C(7) substituent. The orientations of these coplanes to the cephem moiety vary such that the rotation of the cephem C(7) side chain seems not to be rigidly constrained. The exocyclic amido groups in both CZX and CZX-HCl are also planar, with intermolecular hydrogen bonds between the nitrogen and the oxygen atoms of adjacent molecules. The conformations resemble those described for the peptide bond moiety in proteins.

Keywords——ceftizoxime; cephalosporin antibiotic; X-ray analysis; molecular conformation; crystal structure

Introduction

Ceftizoxime,[1] (6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, is a new cephalosporin antibiotic characterized by an aminothiazolyl-methoxyimino group in the C(7) side chain but with no substituent at the C(3) position. The chemical structure and atomic numbering of ceftizoxime are shown in Fig. 1.

This compound displays very potent antibacterial activity with a broad spectrum (including β-lactamase-producing bacteria), characteristics attributable to the stereochemistry of the oxyimino group in the C(7) side chain. This type of cephalosporin generally has 4—32 times greater antibiotic activity in the *syn* configuration (I) than in the *anti* configuration (II),[1] suggesting that geometrical isomerism of the oxyimino group contributes to the structural specificity for antibacterial activity. To investigate conformational features and to clarify the properties of the C(7) side chain, we have undertaken X-ray crystallographic studies of a series of cephalosporins with the *anti* oxyimino group.

We report here the crystal and molecular structures of ceftizoxime (CZX) and its monohydrochloride monohydrate (CZX-HCl), and briefly compare them with those of other cephalosporins which possess the same C(7) substituent, RU25159,[2] cefmenoxime A

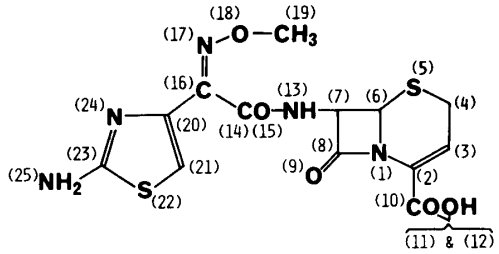

Fig. 1. Ceftizoxime Molecule and Atomic Numbering

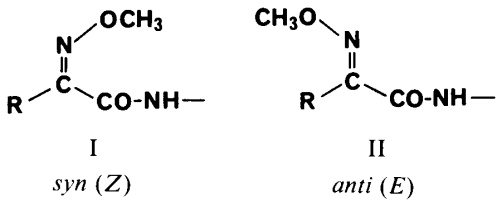

Chart 1

[cefmenoxime hydrochloride molecule (CMX A)] and cefmenoxime B [cefmenoxime molecule (CMX B)].[3]

We are also carrying out the X-ray structure analysis of sodium ceftizoxime, and preliminary results have been published elsewhere.[4] The details of the analysis will be reported in the near future.

Experimental

X-Ray Analysis——Both CZX and CZX-HCl crystallized as colorless, rod-like crystals in the orthorhombic space group $P2_12_12_1$ (CZX from an acidified aqueous solution of the sodium salt, CZX-HCl from an acetonitrile, chloroform, methanol and hydrochloric acid solution of the sodium salt). Crystal data for CZX and CZX-HCl are shown in Table I. Crystal densities were determined by a flotation method.

The intensities of 1556 independent reflections up to $2\theta = 125°$ for CZX and 1876 reflections for CZX-HCl were collected on a Rigaku AFC-5 diffractometer with graphite-monochromated CuK_α radiation. Corrections were applied for Lorentz and polarization factors but not for absorption and extinction, because the crystal sizes were small (CZX, $0.10 \times 0.30 \times 0.35$ mm; CZX-HCl, $0.10 \times 0.10 \times 0.22$ mm).

Structure Determination and Refinement——The structure of CZX was solved by a direct method using the MULTAN 74 program,[5] the positions for all CZX non-hydrogen atoms being successfully assigned. The structure was refined by a block-diagonal matrix least-squares method.[6] The positions of all hydrogen atoms were determined from a difference Fourier synthesis. After further refinement with anisotropic temperature factors for all non-hydrogen atoms and isotropic temperature factors for hydrogen atoms, the final R factor was 0.074 for 1404 non-zero reflections.

The structure of CZX-HCl was solved by a combination of the direct method using the MULTAN 74 program[5] and the Fourier technique. From an E-map using one set of phases with a high value of figure of merit, the positions of most CZX non-hydrogen atoms could be assigned. Successive Fourier syntheses revealed the positions of the remaining non-hydrogen atoms, including the water oxygen and chlorine atoms, in the crystal. The structure was refined by a block-diagonal least-squares method.[6] The positions of hydrogen atoms were determined from a

Table I. Crystal Data

	CZX	CZX-HCl
Chemical formula	$C_{13}H_{13}N_5O_5S_2$	$C_{13}H_{13}N_5O_5S_2 \cdot HCl \cdot H_2O$
Formula weight	383.40	437.87
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Z	4	4
a (Å)	4.950 (1)	4.5626 (3)
b (Å)	14.848 (2)	15.726 (1)
c (Å)	22.258 (4)	27.314 (2)
V (Å^3)	1635.9 (5)	1959.8 (2)
μ (CuK_α) (mm^{-1})	3.241	4.078
λ (Å)	1.5418	1.5418
D_m (Mgm^{-3})	1.520 (2)	1.488 (1)
D_x (Mgm^{-3})	1.557	1.484

difference Fourier synthesis, but those of two water hydrogen atoms could not be determined. After further refinement with anisotropic temperature factors for all non-hydrogen atoms and isotropic temperature factors for hydrogen atoms, the final R factor was 0.076 for 1356 non-zero reflections.

The quantity minimized was $\Sigma w(|F_o|-k|F_c|)^2$, $(w=1)$. The atomic scattering factors cited in the International Tables for X-Ray Crystallography Vol. IV[7] were used. All computations were carried out on a FACOM M-150F computer at our Central Research Laboratories.

TABLE II. Final Atomic Coordinates and Isotropic Thermal Parameters (Å^2) with the Estimated Standard Deviations in Parentheses

Atom	CZX				CZX-HCl			
	x	y	z	B (Å^2)	x	y	z	B (Å^2)
N(1)	0.5979 (15)	0.5585 (5)	0.2734 (3)	2.0	0.1136 (26)	0.4602 (6)	0.3770 (3)	2.3
C(2)	0.4680 (21)	0.5171 (6)	0.2256 (4)	2.5	0.2361 (34)	0.5005 (8)	0.3355 (4)	2.7
C(3)	0.5178 (23)	0.4298 (7)	0.2130 (4)	3.4	0.2345 (41)	0.5862 (8)	0.3322 (5)	3.9
C(4)	0.7095 (26)	0.3692 (7)	0.2470 (5)	3.9	0.1333 (50)	0.6481 (9)	0.3687 (5)	4.4
S(5)	0.7421 (6)	0.4022 (2)	0.3259 (1)	3.2	0.1183 (10)	0.6039 (2)	0.4313 (1)	3.1
C(6)	0.8235 (20)	0.5170 (6)	0.3066 (4)	2.5	−0.0684 (35)	0.5062 (8)	0.4138 (5)	2.9
C(7)	0.7779 (21)	0.5888 (6)	0.3572 (3)	2.3	−0.0110 (29)	0.4270 (8)	0.4481 (4)	2.1
C(8)	0.5361 (20)	0.6201 (6)	0.3194 (4)	2.2	0.2102 (32)	0.3982 (8)	0.4084 (4)	2.5
O(9)	0.3562 (15)	0.6744 (4)	0.3258 (3)	3.3	0.4032 (23)	0.3457 (5)	0.4064 (3)	2.7
C(10)	0.2688 (22)	0.5708 (7)	0.1895 (4)	2.9	0.3436 (40)	0.4475 (9)	0.2933 (5)	3.5
O(11)	0.2380 (18)	0.6497 (4)	0.1986 (3)	4.1	0.2619 (28)	0.3664 (6)	0.2974 (3)	4.3
O(12)	0.1382 (16)	0.5230 (5)	0.1499 (3)	4.1	0.4753 (34)	0.4762 (6)	0.2593 (4)	5.5
N(13)	0.7118 (15)	0.5595 (5)	0.4162 (3)	2.0	0.1231 (25)	0.4442 (6)	0.4963 (3)	2.1
C(14)	0.8994 (20)	0.5418 (6)	0.4559 (4)	2.3	−0.0504 (32)	0.4556 (9)	0.5348 (5)	2.9
O(15)	1.1432 (14)	0.5433 (5)	0.4429 (3)	3.8	−0.3134 (22)	0.4436 (8)	0.5350 (3)	4.7
C(16)	0.8085 (19)	0.5159 (6)	0.5161 (3)	2.0	0.1029 (30)	0.4820 (8)	0.5810 (4)	2.0
N(17)	0.6715 (19)	0.5649 (5)	0.5529 (4)	3.2	0.1658 (30)	0.5602 (7)	0.5907 (4)	3.1
O(18)	0.6214 (20)	0.6498 (4)	0.5272 (3)	4.3	0.0701 (28)	0.6144 (6)	0.5532 (3)	4.2
C(19)	0.4449 (37)	0.6986 (8)	0.5681 (6)	6.8	0.2140 (53)	0.6974 (9)	0.5601 (6)	5.7
C(20)	0.8760 (19)	0.4244 (6)	0.5387 (3)	2.0	0.2010 (31)	0.4179 (8)	0.6164 (4)	2.4
C(21)	1.0674 (24)	0.3718 (6)	0.5155 (4)	2.9	0.1381 (38)	0.3353 (8)	0.6175 (4)	2.8
S(22)	1.0817 (6)	0.2709 (2)	0.5541 (1)	2.7	0.3126 (10)	0.2857 (2)	0.6660 (1)	3.4
C(23)	0.8208 (20)	0.3072 (7)	0.5996 (4)	2.7	0.4701 (38)	0.3805 (9)	0.6836 (5)	3.4
N(24)	0.7330 (16)	0.3899 (4)	0.5878 (3)	2.2	0.3868 (26)	0.4438 (6)	0.6547 (3)	2.2
N(25)	0.7103 (18)	0.2558 (5)	0.6426 (4)	3.5	0.6499 (31)	0.3898 (7)	0.7216 (4)	3.6
Cl					0.3657 (11)	0.2619 (2)	0.2102 (1)	3.5
O(W)					0.8864 (31)	0.4030 (7)	0.1814 (4)	5.8
H(3)	0.492 (23)	0.417 (7)	0.162 (4)	2.3	0.243 (40)	0.617 (10)	0.300 (5)	4.3
H(4a)	0.646 (24)	0.305 (7)	0.245 (4)	2.7	−0.055 (40)	0.690 (9)	0.345 (5)	3.8
H(4b)	0.933 (25)	0.384 (7)	0.235 (4)	2.6	0.296 (44)	0.696 (10)	0.375 (6)	5.1
H(6)	1.021 (21)	0.529 (6)	0.285 (4)	2.1	−0.280 (38)	0.516 (9)	0.395 (5)	2.8
H(7)	0.984 (23)	0.631 (6)	0.360 (4)	2.1	−0.192 (36)	0.380 (9)	0.451 (5)	2.4
H(11)					0.347 (49)	0.326 (11)	0.263 (6)	6.0
H(12)	−0.031 (26)	0.559 (7)	0.131 (5)	3.0				
H(13)	0.534 (22)	0.556 (6)	0.422 (4)	2.2	0.341 (47)	0.448 (10)	0.499 (6)	5.5
H(19a)	0.528 (23)	0.702 (7)	0.612 (4)	3.3	0.167 (44)	0.721 (10)	0.532 (5)	4.5
H(19b)	0.394 (29)	0.760 (8)	0.555 (5)	5.2	0.072 (45)	0.721 (10)	0.582 (6)	5.1
H(19c)	0.298 (28)	0.648 (8)	0.571 (5)	4.4	0.401 (42)	0.696 (9)	0.573 (5)	3.8
H(21)	1.159 (22)	0.376 (6)	0.477 (4)	2.1	−0.008 (43)	0.298 (10)	0.593 (6)	4.7
H(24)					0.489 (38)	0.494 (9)	0.657 (5)	3.4
H(25a)	0.576 (27)	0.295 (7)	0.660 (5)	3.4	0.575 (49)	0.432 (11)	0.744 (6)	6.0
H(25b)	0.841 (28)	0.238 (8)	0.672 (5)	5.2	0.708 (34)	0.342 (8)	0.741 (4)	2.4

$B_{eq}=\frac{4}{3}\left(\frac{B_{11}}{a^{*2}}+\frac{B_{22}}{b^{*2}}+\frac{B_{33}}{c^{*2}}\right)$ for non-hydrogen atoms.

TABLE III. Bond Lengths (Å) and Bond Angles (°) with the Estimated Standard Deviations in Parentheses

	CZX	CZX-HCl		CZX	CZX-HCl
a) Bond lengths (Å)					
N(1)–C(2)	1.387 (13)	1.415 (20)	C(3)–H(3)	1.15 (11)	1.01 (18)
N(1)–C(6)	1.474 (13)	1.490 (20)	C(4)–H(4a)	1.01 (12)	1.15 (19)
N(1)–C(8)	1.406 (12)	1.370 (19)	C(4)–H(4b)	1.16 (12)	1.07 (20)
C(2)–C(3)	1.349 (15)	1.351 (24)	C(6)–H(6)	1.11 (11)	1.11 (17)
C(2)–C(10)	1.500 (15)	1.503 (24)	C(7)–H(7)	1.20 (11)	1.11 (16)
C(3)–C(4)	1.511 (17)	1.468 (29)	O(11)–H(11)		1.19 (23)
C(4)–S(5)	1.829 (13)	1.847 (23)	O(12)–H(12)	1.08 (13)	
S(5)–C(6)	1.804 (10)	1.820 (17)	N(13)–H(13)	0.89 (11)	1.00 (22)
C(6)–C(7)	1.566 (14)	1.581 (21)	C(19)–H(19a)	1.07 (12)	0.89 (20)
C(7)–C(8)	1.535 (14)	1.550 (20)	C(19)–H(19b)	0.99 (14)	0.96 (21)
C(7)–N(13)	1.422 (13)	1.476 (18)	C(19)–H(19c)	1.05 (14)	0.92 (19)
C(8)–O(9)	1.209 (12)	1.208 (18)	C(21)–H(21)	0.97 (11)	1.11 (20)
C(10)–O(11)	1.199 (14)	1.333 (22)	N(24)–H(24)		0.92 (17)
C(10)–O(12)	1.304 (13)	1.195 (24)	N(25)–H(25a)	0.97 (13)	0.96 (22)
N(13)–C(14)	1.309 (12)	1.328 (18)	N(25)–H(25b)	0.95 (14)	0.96 (15)
C(14)–O(15)	1.241 (12)	1.215 (19)			
C(14)–C(16)	1.465 (13)	1.502 (20)			
C(16)–N(17)	1.289 (13)	1.291 (19)			
C(16)–C(20)	1.486 (13)	1.467 (20)			
N(17)–O(18)	1.407 (14)	1.401 (19)			
O(18)–C(19)	1.455 (21)	1.473 (28)			
C(20)–C(21)	1.333 (15)	1.331 (22)			
C(20)–N(24)	1.398 (12)	1.405 (19)			
C(21)–S(22)	1.728 (12)	1.730 (18)			
S(22)–C(23)	1.727 (10)	1.724 (18)			
C(23)–N(24)	1.330 (13)	1.326 (21)			
C(23)–N(25)	1.341 (13)	1.331 (23)			
b) Bond angles (°)					
C(2)–N(1)–C(6)	123.4 (8)	122.9 (12)	C(2)–C(3)–H(3)	110 (6)	122 (10)
C(2)–N(1)–C(8)	138.2 (8)	133.9 (13)	C(4)–C(3)–H(3)	117 (6)	107 (10)
C(6)–N(1)–C(8)	94.1 (7)	96.0 (11)	C(3)–C(4)–H(4a)	110 (7)	112 (9)
N(1)–C(2)–C(3)	120.1 (9)	119.9 (15)	C(3)–C(4)–H(4b)	112 (6)	111 (11)
N(1)–C(2)–C(10)	118.7 (9)	119.7 (13)	S(5)–C(4)–H(4a)	109 (7)	120 (9)
C(3)–C(2)–C(10)	121.3 (10)	120.3 (15)	S(5)–C(4)–H(4b)	95 (6)	98 (11)
C(2)–C(3)–C(4)	125.6 (10)	128.1 (18)	H(4a)–C(4)–H(4b)	118 (9)	100 (14)
C(3)–C(4)–S(5)	112.2 (9)	113.1 (15)	N(1)–C(6)–H(6)	113 (6)	104 (9)
C(4)–S(5)–C(6)	92.5 (5)	95.3 (9)	S(5)–C(6)–H(6)	117 (6)	114 (9)
N(1)–C(6)–S(5)	110.2 (7)	109.0 (10)	C(7)–C(6)–H(6)	110 (6)	122 (9)
N(1)–C(6)–C(7)	88.1 (7)	85.7 (11)	C(6)–C(7)–H(7)	106 (5)	116 (8)
S(5)–C(6)–C(7)	116.1 (7)	115.6 (11)	C(8)–C(7)–H(7)	122 (5)	110 (8)
C(6)–C(7)–C(8)	85.7 (7)	85.6 (10)	N(13)–C(7)–H(7)	108 (5)	111 (8)
C(6)–C(7)–N(13)	119.2 (8)	117.0 (11)	C(10)–O(11)–H(11)		111 (11)
C(8)–C(7)–N(13)	114.8 (8)	114.1 (11)	C(10)–O(12)–H(12)	113 (7)	
N(1)–C(8)–C(7)	91.8 (7)	91.1 (11)	C(7)–N(13)–H(13)	113 (7)	119 (12)
N(1)–C(8)–O(9)	132.8 (9)	133.8 (14)	C(14)–N(13)–H(13)	126 (7)	122 (12)
C(7)–C(8)–O(9)	135.4 (9)	134.9 (13)	O(18)–C(19)–H(19a)	111 (6)	99 (13)
C(2)–C(10)–O(11)	120.9 (10)	112.0 (15)	O(18)–C(19)–H(19b)	115 (8)	97 (12)
C(2)–C(10)–O(12)	113.5 (9)	123.4 (17)	O(18)–C(19)–H(19c)	96 (8)	117 (12)
O(11)–C(10)–O(12)	125.6 (10)	124.6 (17)	H(19a)–C(19)–H(19b)	110 (10)	103 (18)
C(7)–N(13)–C(14)	121.5 (8)	118.9 (11)	H(19a)–C(19)–H(19c)	104 (10)	125 (18)
N(13)–C(14)–O(15)	121.9 (9)	124.8 (14)	H(19b)–C(19)–H(19c)	120 (11)	112 (17)
N(13)–C(14)–C(16)	116.9 (8)	115.2 (12)	C(20)–C(21)–H(21)	129 (6)	129 (10)
O(15)–C(14)–C(16)	121.1 (9)	120.0 (13)	S(22)–C(21)–H(21)	119 (6)	120 (10)

Table III. (continued)

	CZX	CZX-HCl		CZX	CZX-HCl
C(14)–C(16)–N(17)	126.5 (9)	122.6 (13)	C(20)–N(24)–H(24)		127 (11)
C(14)–C(16)–C(20)	118.7 (8)	120.5 (12)	C(23)–N(24)–H(24)		117 (11)
N(17)–C(16)–C(20)	114.8 (9)	116.9 (13)	C(23)–N(25)–H(25a)	103 (8)	110 (13)
C(16)–N(17)–O(18)	109.8 (9)	111.2 (13)	C(23)–N(25)–H(25b)	112 (8)	121 (9)
N(17)–O(18)–C(19)	107.2 (10)	107.8 (14)	H(25a)–N(25)–H(25b)	111 (11)	107 (16)
C(16)–C(20)–C(21)	124.4 (9)	128.3 (14)			
C(16)–C(20)–N(24)	119.0 (8)	118.4 (12)			
C(21)–C(20)–N(24)	116.6 (9)	113.4 (13)			
C(20)–C(21)–S(22)	110.2 (8)	111.0 (13)			
C(21)–S(22)–C(23)	89.4 (5)	90.9 (8)			
S(22)–C(23)–N(24)	114.6 (7)	111.3 (12)			
S(22)–C(23)–N(25)	123.1 (8)	124.7 (13)			
N(24)–C(23)–N(25)	122.2 (9)	124.0 (16)			
C(20)–N(24)–C(23)	109.1 (8)	113.5 (13)			

Results and Discussion

The final atomic coordinates and isotropic thermal parameters are given in Table II. The bond lengths and angles are listed in Table III, and selected torsion angles in CZX and CZX-HCl as well as RU25159 and CMX A and B are listed in Table IV.

Molecular Conformation

The molecular conformations of CZX and CZX-HCl drawn with the ORTEP II program[8] are presented in Fig. 2 and those of RU25159 and CMX A and B in Fig. 3. The conformational features of these molecules are similar except for different rotation angles around the C(14)–C(16) bond, where the torsion angles of N(13)–C(14)–C(16)–C(20) are 117°, −92°, 85°, −124° and −62° for CZX, CZX-HCl, RU25159 and CMX A and B, respectively as shown in Table IV.

The C(7) Side Chain

In both CZX and CZX-HCl molecules, the aminothiazole ring is of an amino- rather

Table IV. Selected Torsion Angles (°)

	CZX	CZX-HCl	RU25159	CMX A	CMX B
C(6)–C(7)–N(13)–C(14)	89	93	120	74	88
C(8)–C(7)–N(13)–C(14)	−171	−169	−151	−174	−178
C(7)–N(13)–C(14)–O(15)	−5	9	0	−2	−2
C(7)–N(13)–C(14)–C(16)	177	−174	175	177	175
N(13)–C(14)–C(16)–N(17)	−63	85	−106	60	110
N(13)–C(14)–C(16)–C(20)	117	−92	85	−124	−62
O(15)–C(14)–C(16)–N(17)	120	−98	68	−121	−72
O(15)–C(14)–C(16)–C(20)	−60	85	−101	56	116
C(14)–C(16)–N(17)–O(18)	−1	1	16	−2	1
C(20)–C(16)–N(17)–O(18)	180	178	−175	178	174
C(16)–N(17)–O(18)–C(19)	175	−165	−176	−168	173
C(14)–C(16)–C(20)–C(21)	18	−11	−3	−7	−15
C(14)–C(16)–C(20)–N(24)	−163	169	176	171	165
N(17)–C(16)–C(20)–C(21)	−163	172	−173	170	172
N(17)–C(16)–C(20)–N(24)	17	−8	6	−12	−8

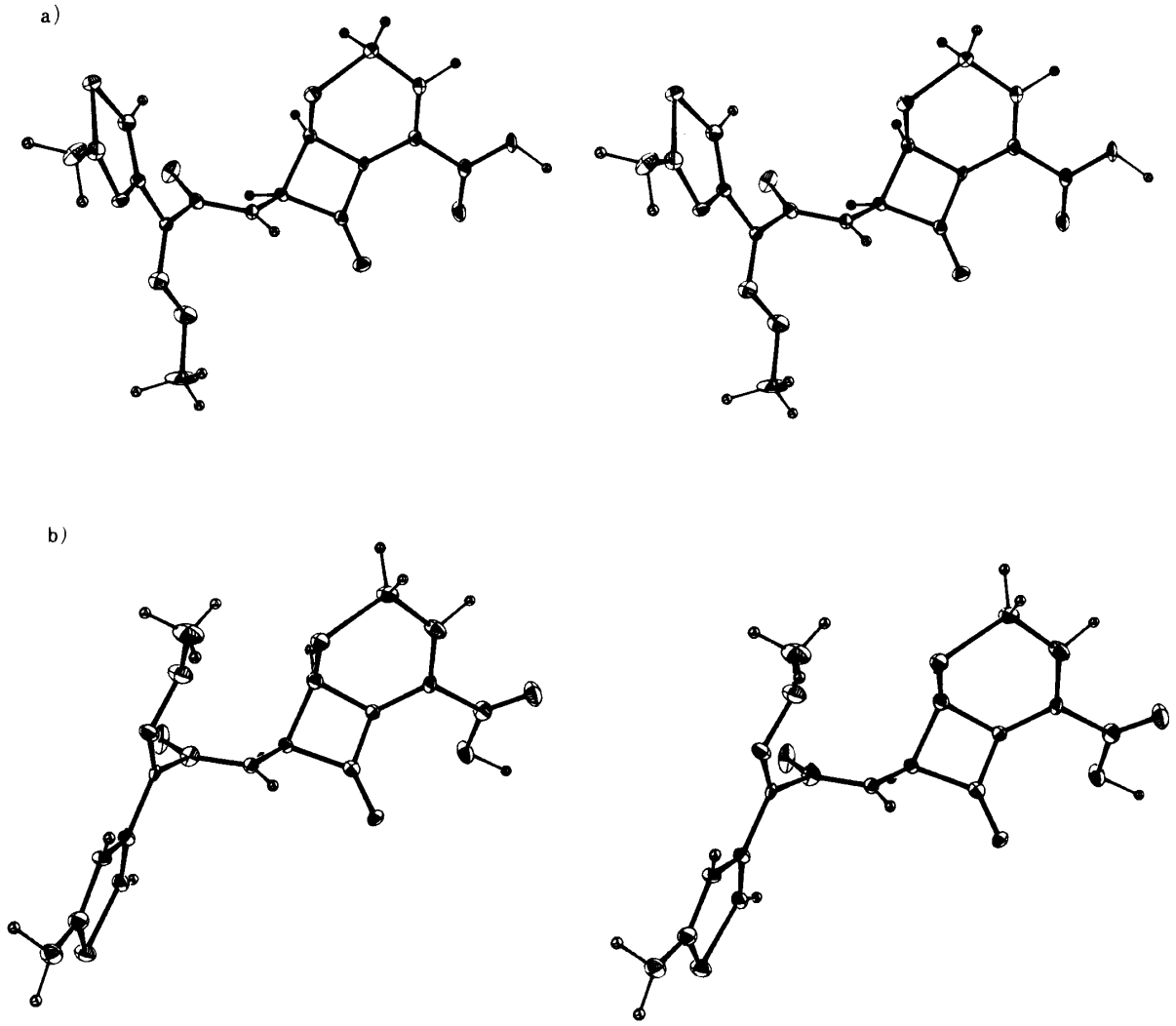

Fig. 2. Stereographic Molecular Conformations of CZX and CZX-HCl after a Least-Squares Fitting of Atoms C(2), C(6) and C(8)
a) CZX, b) CZX-HCl.

than imino-type, and participates in intermolecular hydrogen-bond formation.

In CZX, as shown in Fig. 4a, N(25) donates a hydrogen to O(11) of an adjacent molecule, and N(24) accepts a hydrogen from O(12) of that molecule, that is, the hydrogen of the carboxyl group at the C(2) position is localized at O(12).

In CZX-HCl, however, as shown in Fig. 4b, N(25) donates a hydrogen to a chlorine anion, and N(24) is protonated so that it donates that hydrogen to oxygen of the water molecule.

The bond distance of N(25)–C(23) is nearly equal to that of N(24)–C(23) for both CZX and CZX-HCl. This is also observed in other cephalosporins, as shown in Table V.

The aminothiazole ring and the methoxyimino group are planar within the experimental deviation in CZX and CZX-HCl as well as in RU25159[2] and CMX A and B[3]; moreover, these two groups are obviously quasi coplanar (Figs. 2 and 3). The dihedral angles between these two mean planes are 18 ° for CZX, 10 ° for CZX-HCl, 2 ° for RU25159, 10 ° for CMX A and 11 ° for CMX B (Table VI). The coplanarity of the aminothiazole ring and the methoxyimino group seems to be a common characteristic for all cephalosporins of this type. However the coplanar orientation with respect to the cephem moiety differs greatly due to

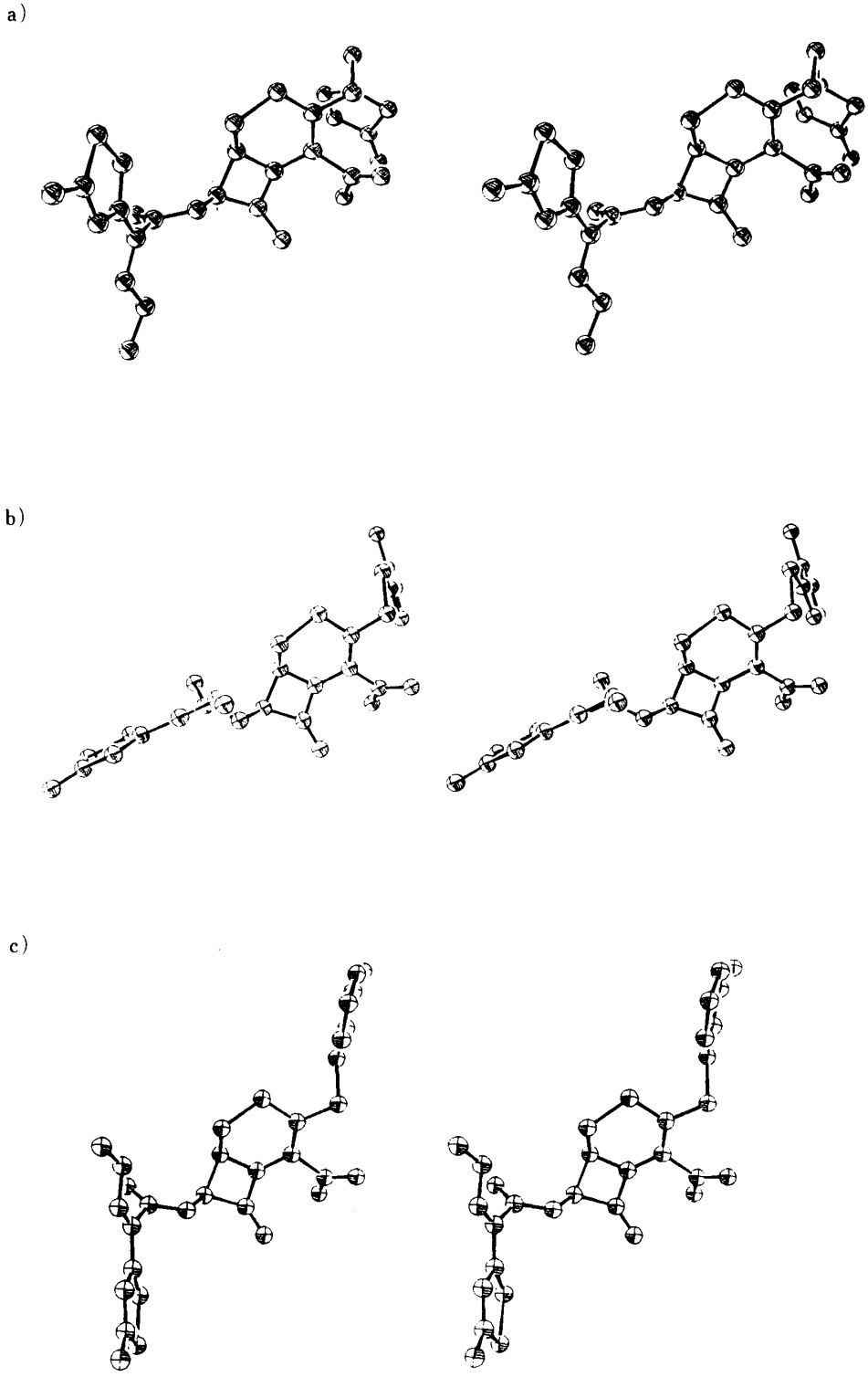

Fig. 3. Stereographic Molecular Conformations of RU25159, Cefmenoxime A and B after Least-Squares Fitting of Their β-Lactam Ring

a) RU25159, b) CMX A, c) CMX B.

rotation around the C(14)–C(16) bond (Table IV). Lacking any intrahydrogen bonds to stabilize this coplanarity, the coplane in these molecules is likely to easily adopt various orientations due to the various packing forces and the formation of intermolecular hydrogen bonds in the aminothiazole ring. The varied orientations of these coplanes observed in the

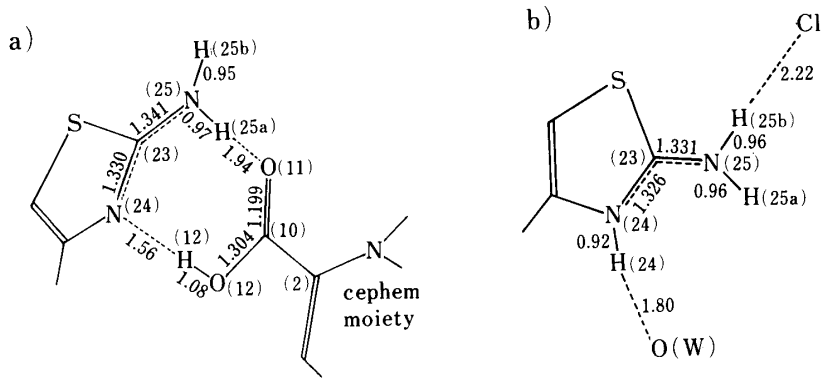

Fig. 4. Aminothiazole Moieties of CZX and CZX-HCl
a) CZX, b) CZX-HCl.

TABLE V. Bond Distances (Å) between C and N Atoms in the Aminothiazole Ring

	C(23)–N(25)	N(25)	C(23)–N(24)	N(24)
CZX	1.34	$-NH_2$	1.33	H-Accepter
CZX-HCl	1.33	$-NH_2$	1.33	Protonation
RU25159	1.40	Unknown	1.38	Unknown
CMX A	1.31	$-NH_2$	1.33	Protonation
CMX B	1.33	$-NH_2$	1.31	Non-H atom

TABLE VI. Dihedral Angles (°) between Best Planes

	CZX	CZX-HCl	RU25159	CMX A	CMX B
[1]–[2]	18	10	2	10	11
[1]–[3]	55	81	83	55	71
[2]–[3]	61	83	81	59	68

[1] Plane through C(20), C(21), S(22), C(23) and N(24), aminothiazole ring. [2] Plane through C(14), C(16), N(17), Q(18) and C(20), oxyimino group. [3] Plane through C(7), N(13), C(14), O(15) and C(16), exocyclic amido function.

crystal state may suggest that the differences in potential energy for such conformational changes are so small that the rotation of the C(7) side chain with respect to the cephem moiety is not rigidly constrained. A similar idea has been proposed by Laurent *et al.*[2]

Generally the *syn* oxyimino group seems to be able to form a coplane together with the aminothiazole ring.[2-4] The orientation of this bulky coplane may be flexible, which may have something to do with protecting the β-lactam moiety from β-lactamases. Analysis of the *anti* oxyimino isomer should be helpful in establishing the validity of this hypothesis.

The Exocyclic Amino Moiety

The exocyclic amido groups of both CZX and CZX-HCl at the C(7) position are also planar within the experimental deviation, such that the O(15) and H(13) atoms are *trans* to one another, showing that the N(13) atom takes the sp^2 hybrid orbital. The bond distance between N(13) and C(14) is somewhat shorter than the usual C–N single bond distance (1.472 Å),[9] *i.e.* 1.31 Å (CZX) and 1.33 Å (CZX-HCl), acting somewhat like a double bond and thus unable to rotate freely. Intermolecular hydrogen bonds are observed between the N(13)

and O(15) atoms. These are the same properties as proposed for the peptide bond moiety in proteins by Pauling *et al.*[10]

Packing and Hydrogen Bonds

Figure 5 shows the molecular packing diagrams of CZX and CZX-HCl drawn with the PLUTO program,[11] viewed along the *a* axis. The principal intermolecular hydrogen bond distances are listed in Table VII. The exocyclic amido groups at the C(7) position have intermolecular hydrogen bonds between N(13) and O(15) that link the molecules along the *a* axis in both CZX and CZX-HCl.

In CZX, two other hydrogen bonds, N(25)–H(25a)···O(11) [2.91 Å] and N(24)···H(12)–O(12) [2.64 Å] extend the crystal along the *c* axis, and there is one van der

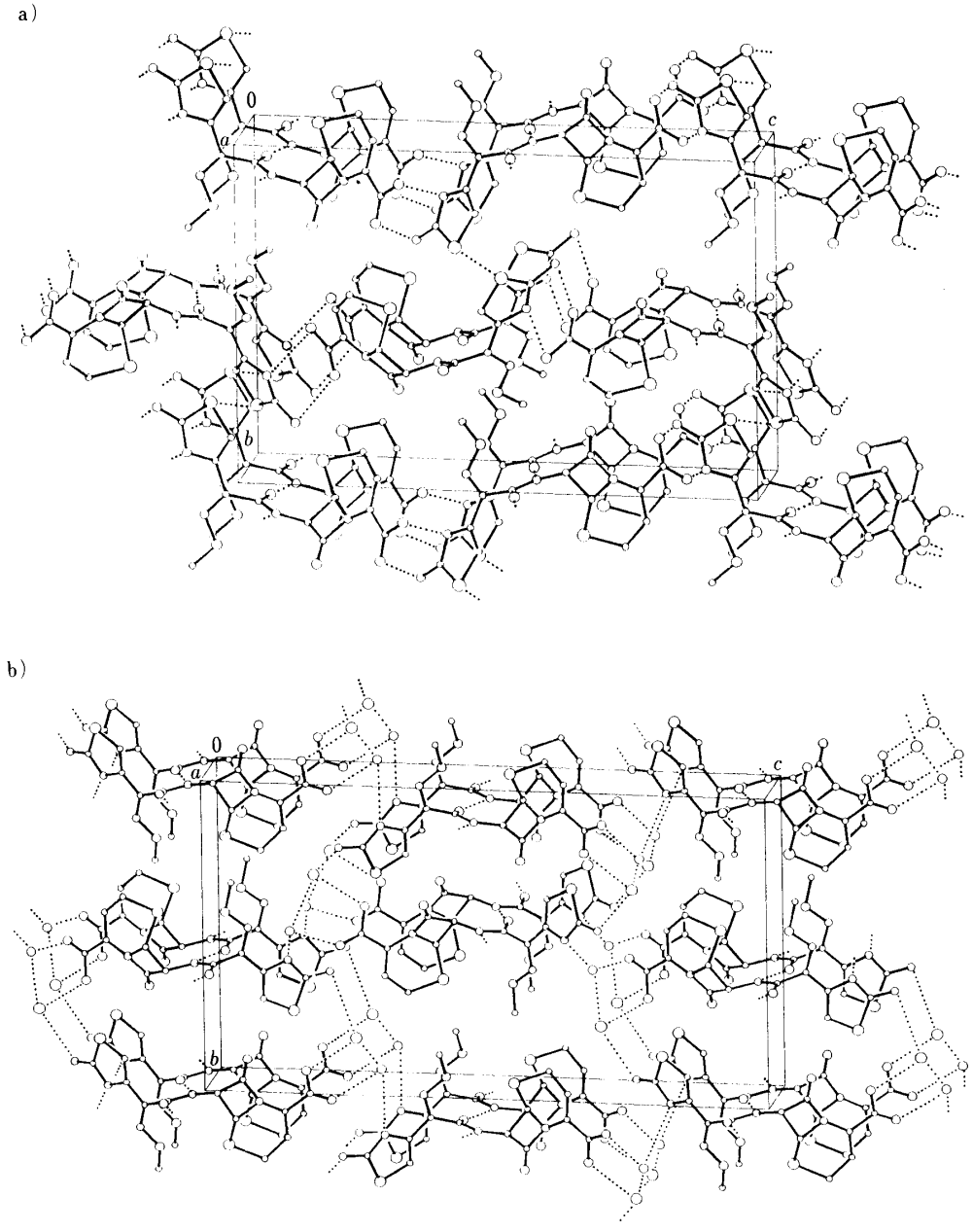

Fig. 5. Molecular Packing Diagrams of CZX and CZX-HCl

The dotted lines indicate the hydrogen bonds or van der Waals short contacts.
a) CZX, b) CZX-HCl.

TABLE VII. Principal Intermolecular Hydrogen-Bond Distances (Å)

CZX				CZX-HCl			
Donor		Acceptor		Donor		Acceptor	
N(13)[a]	····	O(15)	2.89	N(13)	····	O(15)[a]	2.78
N(25)[b]	····	O(11)	2.91	O(11)	····	Cl	2.93
O(12)	····	N(24)[b]	2.64	N(25)[c]	····	Cl	3.18
				N(24)[b]	····	O(W)	2.72

a) $x+1, y, z$. *b*) $-x+0.5, -y+1, -z+1$. *c*) $x+0.5, -y+0.5, -z+1$.

Waals short contact, S(22)···S(22) [3.51 Å]. In CZX-HCl, the chlorine anion and the water oxygen contribute in linking the three molecules by means of hydrogen bonds, *i.e.* Cl···H(25b) [3.18 Å], Cl···H(11)–O(11) [2.93 Å] and OW···H(24)–N(24) [2.72 Å]. Though the water hydrogens could not be found in this structure analysis, the distances of OW···O(12) = 3.06 Å and Cl···OW = 3.25 Å suggest the possibility of hydrogen bonds between them.

These hydrogen bonds and short contacts constitute a three-dimensional network which stabilizes the CZX and CZX-HCl crystals.

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