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Crystal and Molecular Structure of Cefmenoxime Hemihydrochloride

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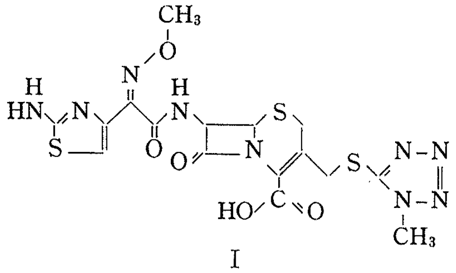
X-ray analysis of cefmenoxime hemihydrochloride was performed. The asymmetric unit of the crystal consists of one chlorine anion and one protonated and one free cefmenoxime molecule. A part of the free molecule is disordered, and conformational differences are observed among the protonated molecule and the two forms of disordered molecules. Intermolecular forces link two independent molecules of cefmenoxime and a chlorine anion and constitute a three-dimensional network in the crystal.

Keywords——cefmenoxime; hemihydrochloride; cephalosporin; crystal structure; molecular conformation; X-ray analysis

Crystallization of 7β-[2-(2-aminothiazol-4-yl)-(z)-2-methoxyiminoacetamido]-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid (cefmenoxime, I, $C_{16}H_{17}N_9O_5S_3$)$^{1)}$ as its hydrochloride gives two different crystalline forms, of which one contains a half molar equivalent and the other contains one molecular equivalent of hydrogen chloride. The former crystal was promising from the standpoint of manufacturing this cephalosporin because of its stable nature and relatively easy crystallization, but the water content in the crystal varied widely depending on the drying conditions. We undertook X-ray analysis in order to clarify whether the water was merely adsorbed or an essential component of the crystal, and to determine the crystal structure of this stable crystal.



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Experimental

Slow evaporative concentration from aqueous acetone solution of cefmenoxime monohydrochloride gave colorless prisms. Elemental analysis suggested that the crystal contained a half molar equivalent of hydrogen chloride. Crystal and reflection data were obtained with a Rigaku AFC-5 diffractometer using MoKα radiation (λ=0.7107 Å). Out of 4268 independent reflections, 2683 reflections had $F \geqq 3\sigma(F)$, and therefore were used in the calculations for structure determination. Computations were performed with an IBM 370/148 computer using the program X-RAY 76.$^{2)}$

Structure Determination

The crystal belongs to the monoclinic system with the space group $P2_1$ and the unit-cell dimensions are a=12.278 (4), b=18.194 (4), c=10.550 Å, β=110.02° (2) and V=2214 (1) Å^3. The calculated density (Dx=1.29 g cm^{-3}) suggests z=4, thus requiring that the asymmetric unit consists of two independent cefmenoxime molecules and one hydrogen chloride.

Based on the atomic coordinates of S and Cl atoms obtained by the Patterson method, the atomic coordinates of the remaining 60 nonhydrogen atoms contained in an asymmetric unit were easily derived by the heavy atom method. These nonhydrogen atoms were found to correspond to those of two molecules of cefmenoxime (tentatively named molecules A and

Table I. Atomic Coordinates ($\times 10^4$) of Nonhydrogen Atoms with Their Standard Deviations

Atom	Molecule A			Molecule B			Molecule B′		
	x/a	y/b	z/c	x/a	y/b	z/c	x/a	y/b	z/c
S (1)	2452(3)	5217(2)	7819(3)	8966(3)	4118(2)	7134(4)			
S (2)	5153(3)	5520(2)	15924(3)	9331(3)	−44(2)	9405(3)			
S (3)	381(3)	3819(2)	3550(4)	7307(4)	5821(3)	3167(6)	8427(11)	5239(7)	3025(11)
O (1)	5810(6)	4168(5)	8653(7)	6814(7)	2283(5)	5172(9)			
O (2)	4508(7)	2946(5)	6396(8)	5112(9)	3344(6)	3034(11)	5238(27)	3557(17)	3072(30)
O (3)	4188(7)	3682(5)	4659(8)	6373(11)	3567(8)	2075(12)	6694(25)	3966(20)	2295(28)
O (4)	3236(6)	4936(5)	11378(8)	8721(7)	2965(5)	10175(8)			
O (5)	3989(7)	6617(5)	10135(8)	11235(6)	3068(4)	10420(8)			
N (1)	3762(7)	4050(5)	7738(8)	6913(7)	3561(5)	5582(9)			
N (2)	4606(7)	5106(5)	10434(8)	8507(8)	2566(6)	8065(8)			
N (3)	4357(8)	6642(5)	11537(9)	11158(7)	2319(5)	10414(9)			
N (4)	5181(7)	6551(5)	14292(8)	10990(6)	873(5)	9991(8)			
N (5)	5943(9)	6887(6)	16577(10)	11632(8)	−330(5)	9947(10)			
N (6)	−56(8)	2366(6)	3453(10)	8863(15)	6847(8)	3118(16)	8418(28)	6755(21)	2923(32)
N (7)	508(11)	1718(7)	3591(13)	10036(15)	6906(12)	3306(18)	9163(33)	7347(21)	3066(35)
N (8)	1573(10)	1855(7)	3867(12)	10449(14)	6256(12)	3616(18)	10115(39)	6901(27)	3399(46)
N (9)	1759(8)	2577(6)	3885(11)	9602(16)	5742(10)	3557(18)	10091(36)	6194(30)	3641(41)
C (1)	1625(11)	4773(7)	6193(12)	8389(14)	4796(9)	5783(18)	8351(37)	5018(21)	6295(39)
C (2)	2359(9)	4325(6)	5601(11)	7562(13)	4482(10)	4426(16)	7650(34)	4732(24)	4953(45)
C (3)	3355(8)	3980(5)	6302(10)	6911(12)	3918(9)	4416(13)	6989(40)	4066(32)	4516(47)
C (4)	3104(9)	4354(6)	8523(10)	7538(8)	3796(7)	6971(10)			
C (5)	4288(8)	4397(6)	9735(10)	7433(9)	2978(7)	7407(10)			
C (6)	4837(8)	4187(6)	8700(10)	6981(9)	2827(7)	5887(12)			
C (7)	4072(8)	3483(6)	5770(10)	6065(15)	3572(10)	3064(15)	6289(32)	3826(30)	3244(51)
C (8)	4014(8)	5295(6)	11237(11)	9039(10)	2593(7)	9403(12)			
C (9)	4365(8)	5991(6)	12015(10)	10087(9)	2086(6)	9929(11)			
C (10)	4215(13)	7321(8)	9646(13)	12419(10)	3249(6)	11114(12)			
C (11)	4692(8)	5944(6)	13488(10)	9985(9)	1302(6)	9778(11)			
C (12)	4609(11)	5352(6)	14207(12)	9030(8)	877(7)	9451(11)			
C (13)	5471(10)	6419(6)	15602(12)	10806(9)	161(7)	9835(11)			
C (14)	1834(10)	4234(7)	4091(12)	7532(19)	4851(13)	3071(22)	7402(32)	5281(24)	3828(34)
C (15)	750(10)	2872(7)	3679(11)	8668(15)	6155(12)	3220(17)	8986(52)	6109(27)	3289(51)
C (16)	−1301(12)	2413(11)	3164(17)	8045(24)	7451(12)	2624(24)	7235(33)	6945(29)	2431(51)
Cl	6414(2)	6031(2)	9337(3)						

Table II. Atomic Coordinates ($\times 10^3$) of Hydrogens with Their Standard Deviations in Parentheses

	Molecule A			Molecule B		
H (11)	121(11)	532(8)	564(13)			
H (12)	109(11)	440(8)	661(13)			
H (O 31)	485(12)	347(8)	422(13)			
H (41)	259(10)	398(7)	853(11)	713(11)	421(8)	747(13)
H (51)	417(10)	402(7)	1038(11)	688(11)	297(8)	789(13)
H (N 21)	518(12)	546(8)	1027(14)	873(12)	228(8)	768(13)
H (101)	393(11)	720(8)	867(13)	1237(11)	374(7)	1104(12)
H (102)	362(10)	764(7)	964(12)	1289(10)	308(8)	1059(12)
H (103)	504(13)	748(8)	1026(14)	1269(11)	316(8)	1207(13)
H (121)	432(11)	481(8)	1380(13)	827(11)	110(8)	940(13)
H (N 51)	615(10)	735(7)	1635(11)	1228(10)	−8(7)	982(12)
H (N 52)	625(12)	681(8)	1763(14)	1147(8)	−92(6)	980(10)
H (N 41)	550(8)	706(6)	1390(9)			
H (141)	233(8)	406(6)	369(10)			
H (142)	168(11)	471(7)	381(13)			
H (161)	−176(11)	269(8)	216(13)			
H (162)	−168(11)	188(8)	341(13)			
H (163)	−142(11)	277(8)	408(13)			

B). After refinement of the atomic coordinates and the temperature factors by the block-diagonal least-squares method, a difference synthesis was carried out to find the hydrogen atoms. The resulting map contained some peaks with electron densities two to five times higher than those of hydrogen atoms. These peaks were attributable to disorder in the crystal. By refining the population parameters of atoms which exist in disordered states, atomic coordinates of hydrogen atoms excluding the disordered part were deduced by subsequent least-squares and difference electron density calculations. Refinement of the atomic coordinates, anisotropic thermal parameters for nonhydrogen atoms, isotropic thermal parameters for hydrogens and population parameters by the unweighted block-diagonal least-squares method gave a final R value of 0.056 for 2683 reflections and 0.069 for all reflections. The final atomic coordinates are given in Tables I and II, in which atomic numbers coincide with those shown in Fig. 1a.

Results and Discussion

Figs. 1a and b represent the conformations of molecule A and two disordered forms of molecule B (B, B'). Figs. 2 and 3 indicate bond lengths and valency angles, respectively. In the present crystal, the asymmetric unit is composed of one chlorine anion and one protonated and one free cefmenoxime molecule. There is no water molecule. A similar crystal structure of the hemihydrochloride was reported for 9-ethylguanine,³⁾ in which the asymmetric unit consists of two ethylguanine moieties and one chlorine anion. This is in contrast to the structures of hydrochlorides of coccinellin,⁴⁾ pelargolactam⁵⁾ and caprinolactam,⁶⁾ where the chlorine anions occupy special positions with less multiplicity.

Positional disorder was found for a part of molecule B; the ratio of population of B and B' was about seven to three. The positional disorder occurs at C(1), C(2) and C(3) of the cephem moiety and the substituents on them. Though only slight positional shifts are detected at C(1), C(2), C(3) and the carboxyl portion, changes in torsional angles about the C(2)–C(14), C(14)–S(3) and S(3)–C(15) bonds lead to dissimilar relative orientations of the cephem and the tetrazole moieties between B and B'. The relative orientations of the cephem and the tetrazole groups found in B and B' also differ from that in A. The dissimilarity between molecules A and B is mainly caused by the torsion about C(14)–S(3), while that between A and B' arises

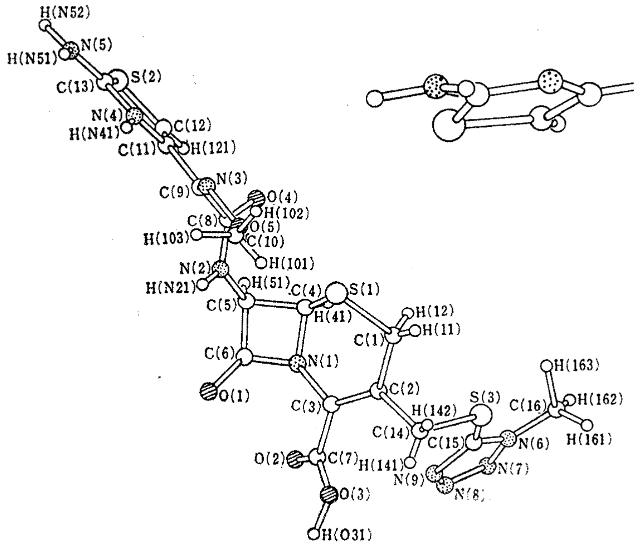

Fig. 1a. Perspective View of Molecule A Projected on the Least-squares Plane of the β-Lactam Ring

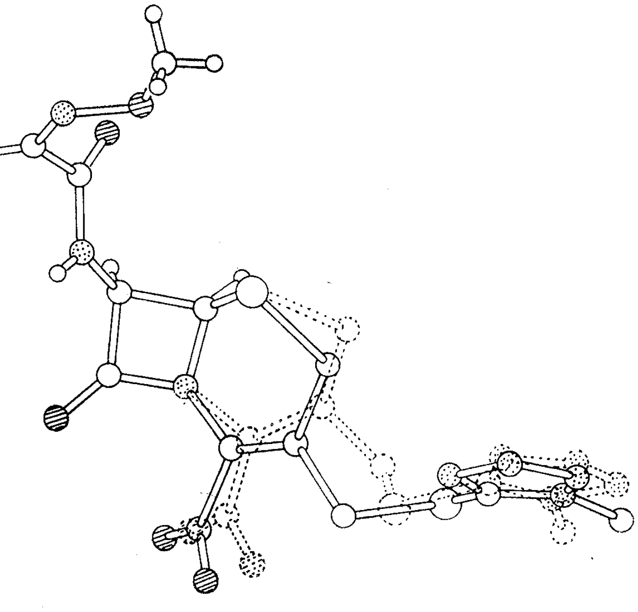

Fig. 1b. Perspective View of Molecules B and B' (Dotted)

from torsion about C(2)–C(14) and S(3)–C(15).

The aminothiazole moiety of molecule A is protonated, that is, two and one hydrogen atoms were found at N(5) and N(4), respectively. As the bond distance of N(5)–C(13) is nearly equal to that of N(4)–C(13), the positive charge seems to be delocalized over N(5), C(13) and N(4). In molecule B, no hydrogen was detected at N(4). Though molecule B is not protonated, close similarity is observed between bond distances of the aminothiazole moiety

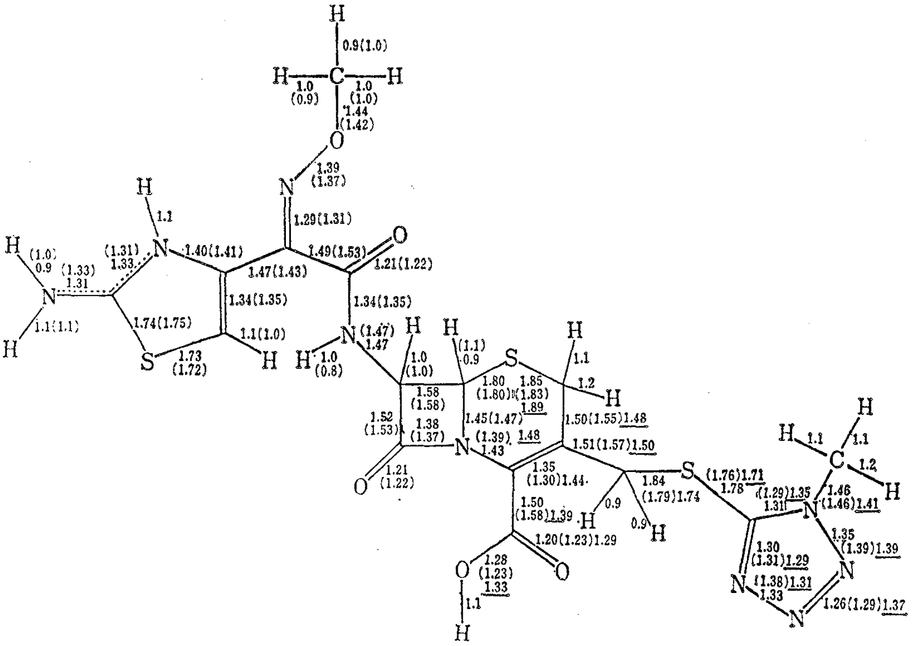

Fig. 2. Bond Lengths (Å) of Molecules A, B (parentheses) and B′ (underlined)

The means of e.s.d.'s for nonhydrogen atoms are 0.015, 0.02 and 0.06 Å for A, B and B′, and those for hydrogen atoms are 0.14 and 0.15 Å for A and B, respectively.

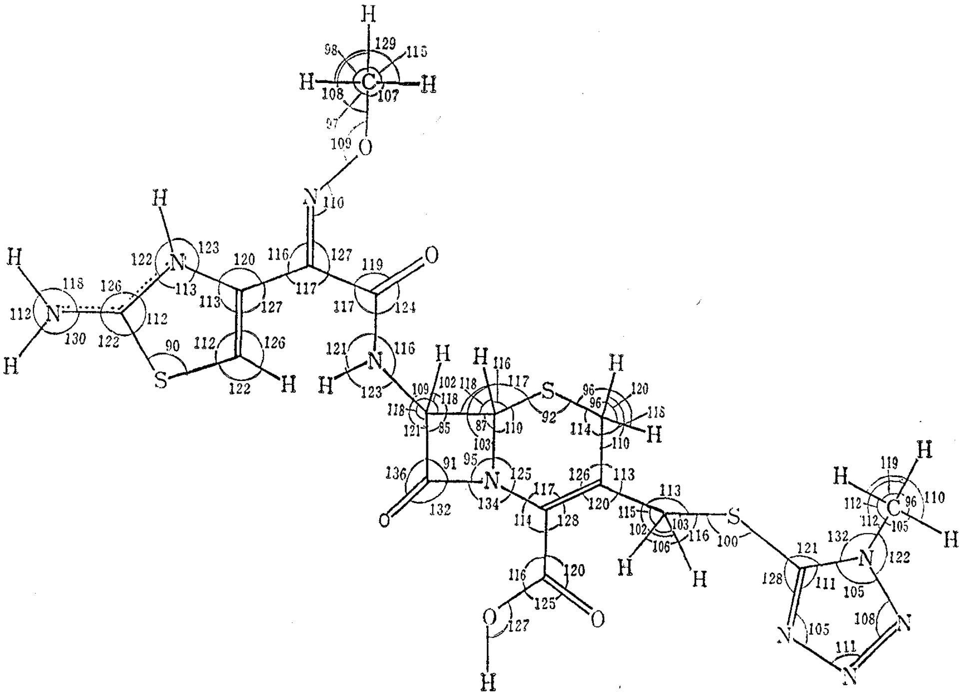

Fig. 3a. Valency Angles of Molecule A (Degrees)

The means of e.s.d.'s concerning nonhydrogen and hydrogen atoms are 0.9° and 8°, respectively.

of B and those of A. The spatial interrelation between the aminothiazole and methoxime groups in A is similar to that in B, but the relative orientations of the aminothiazole and the methoxime groups with respect to the cephem moiety are remarkably different in molecules A and B, due to the rotation around C(8)–C(9). The coexistence of three different molecules of cefmenoxime in the same crystal suggests that such conformational changes may have little influence on the potential energy of cefmenoxime.

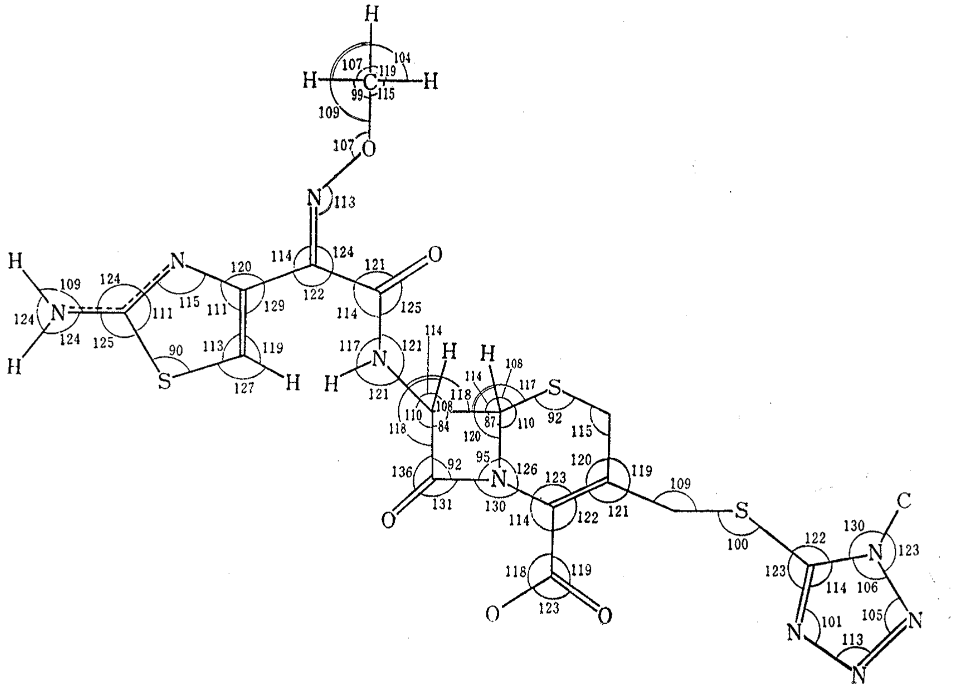

Fig. 3b. Valency Angles of Molecule B

The means of e.s.d.'s, for nonhydrogen and hydrogen atoms are 1.1° and 8°, respectively.

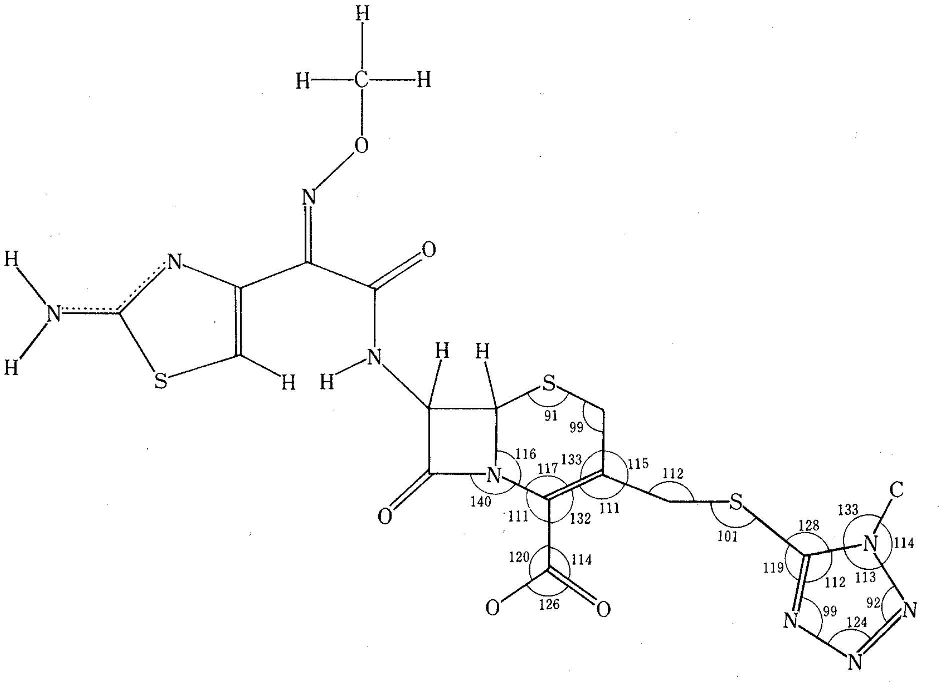

Fig. 3c. Valency Angles of Molecule B′

The mean of e.s.d.'s is 3°.

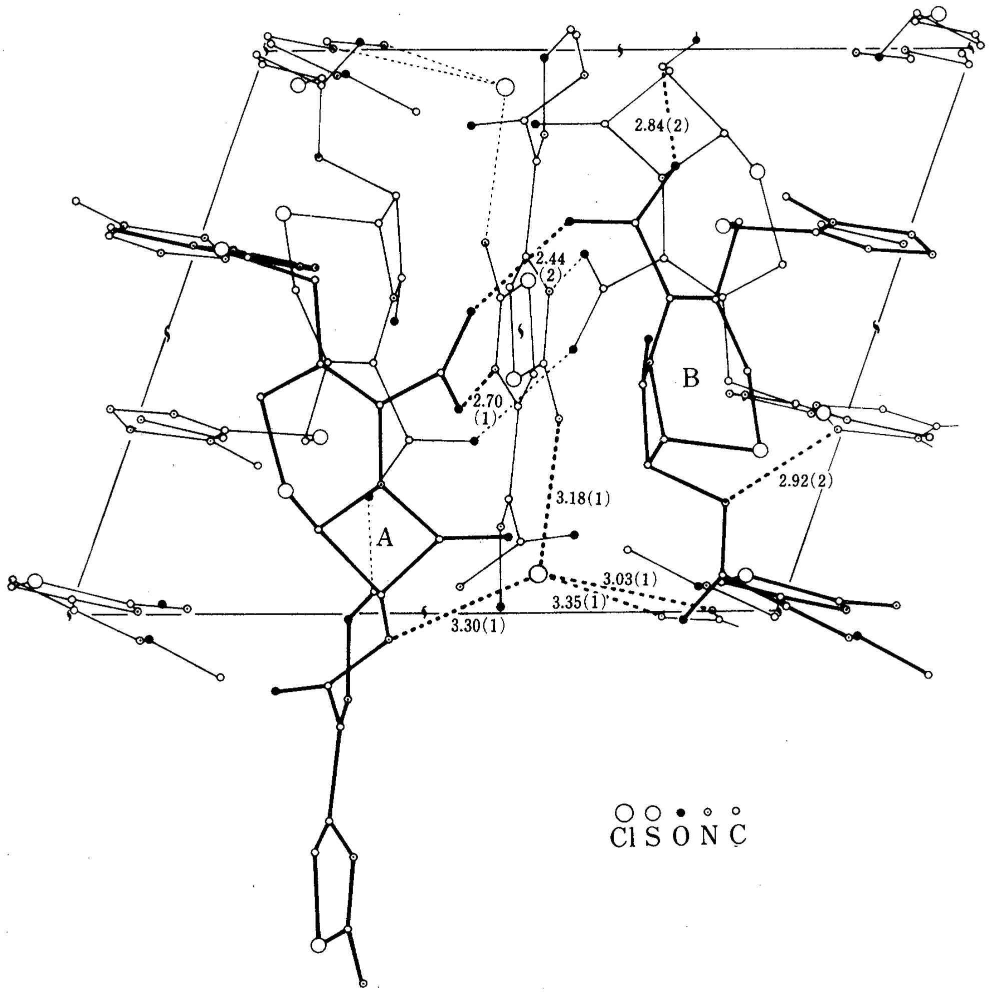

Fig. 4. Packing Diagram of Cefmenoxime Hemihydrochloride

Broken lines represent close intermolecular contacts and numbers are distances (Å) with e.s.d.'s in parentheses.

The molecular packing mode is shown in Fig. 4. In order to avoid complexity, all hydrogen atoms are omitted and only dominant atoms are drawn for the disorded part. As shown in the figure, the chlorine anion is hydrogen bonded to N(2)–H of molecule A and to N(5)–H of another A, which is related to the former A by translation along the *c*-axis. Other contacts are also found between the chlorine anion and N(4) and N(5)–H of B. As for the carboxyl oxygens, O(3)–H of A is hydrogen bonded strongly to O(2) of B, and O(2) of A accepts a hydrogen from N(4) of another A, which is related by the screw at (0.5, *y*, 1.0). A close contact is observed between O(3) of B and C(10) of A. The amide nitrogen N(2) of B donates a hydrogen to N(7) of another B, which is related by the screw at (1.0, *y*, 0.5). In the case of B′, a similar hydrogen bond is found between N(2)–H and N(8) with a distance of 2.91 (2) Å. These intermolecular forces constitute a three-dimensional network which stabilizes the crystal.

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References and Notes

1) M. Ochiai, O. Aki, A. Morimoto, T. Okada, and Y. Matsushita, *Chem. Pharm. Bull.*, **25**, 3115 (1977); M. Ochiai, A. Morimoto, T. Okada, Y. Matsushita, O. Aki, M. Kida, and K. Okonogi, 18th ICAAC, Oct. 2, 1978 (Atlanta, U.S.A.) (Abst. No. 150).

2) J.M. Stewart, Technical Report TR-446 of Computer Science Center, University of Maryland, MD, U.S.A.
3) G.S. Mandel and R.E. Marsh, *Acta Cryst.*, **B31**, 2862 (1975).
4) R. Karlson and D. Losman, *J. Chem. Soc. Chem. Commun.*, **1972**, 626.
5) F.K. Winkler and J.D. Dunitz, *Acta Cryst.*, **B31**, 283 (1975).
6) F.K. Winkler and J.D. Dunitz, *Acta Cryst.*, **B 31**, 286 (1975).