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The Crystal Structure of Acemetacin Monohydrate ($C_{21}H_{18}NO_6Cl \cdot H_2O$), A Non-Steroidal Antiinflammatory Agent

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The molecular structure of acemetacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid carboxymethyl ester, was determined by single crystal X-ray diffraction analysis. The compound was recrystallized from a mixture of acetone and water in triclinic, space group $P\bar{1}$, with $a=7.796(1)$, $b=10.245(2)$, $c=13.542(3)$ Å, $\alpha=97.35(1)$, $\beta=96.34(1)$, $\gamma=107.06(1)$ °, and $Z=2$. The calculated density is 1.422; the observed value is 1.42 g/cm^3. The structure was solved by the direct method and refined by full matrix least-squares procedure to the final R value of 0.037 for 2960 independent reflections. There are water molecules, which are thought to be co-crystallized during the evaporation procedure, with the ratio of one water per compound molecule in the crystal. The conformation of the compound is found to be very similar to that of indomethacin. The molecules are stabilized by three O-H···O type intermolecular hydrogen bonds between the oxygen of water molecule and those of the compound.

Key words: Acemetacin, Antiinflammatory agent, Crystal structure, X-ray diffraction analysis, Hydrogen bond

INTRODUCTION

Acemetacin (Fig. 1), 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid carboxymethyl ester, is one of the non-steroidal antiinflammatory drugs (Flower *et al.*, 1980; Boltze *et al.*, 1980; Hart *et al.*, 1982). The compound is used in gout, rheumatoid arthritis, *etc.*, but it sometimes causes dyspepsia, headache, gastrointestinal and renal toxicities (Flower *et al.*, 1980; Hart *et al.*, 1982). The compound is structurally very similar to indomethacin and cinmetacin.

It has been known that the antiinflammatory agents inhibit prostaglandin biosynthesis, or more specifically the enzyme cyclooxygenase (Bray and Gordon, 1978; Tomlinson *et al.*, 1972). Several models about their modes of interaction with the target site were proposed independently (Gund and Shen, 1977; Appleton and Brown, 1979) but they have not been confirmed at the molecular level yet.

We have determined the three dimensional structures of the non-steroidal antiinflammatory agents (Kim *et al.*, 1986; 1987; 1988; 1989; 1990). And in this paper, we studied the structure of acemetacin to provide precise and useful informations necessary for the receptor modeling and new drug design of the non-steroidal antiinflammatory agents.

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MATERIALS AND METHODS

The compound is kindfully supplied from Boehringer Ingelheim Korea Ltd. Colorless prismatic crystals were grown by the slow evaporation method from a mixture of acetone and water at room temperature. The density was measured by the flotation method in a potassium iodide solution. A crystal of dimensions $0.4\times0.4\times0.2$ mm was mounted on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated MoKα radiations (50 kV, 20 mA, $k=0.7107$ Å). Angular positions of 25 reflections within $8\leq\theta\leq10°$ were centered using a "blind" search procedure, and the lattice constants were determined from the values of these reflections. The crystallographic data are listed in Table I.

Intensity data with range of $-9\leq h\leq9$, $-12\leq k\leq12$, $0\leq l\leq19$ (hkl range within the sphere of $\theta\leq25°$) were collected by ω-2θ scan technique with the scan width of $\Delta\omega=1.0+0.35\tan\theta$ (estimated from ω-θ plots). The counter aperture was also adjusted as a function of θ, the horizontal aperture width ranging from 3.0 to

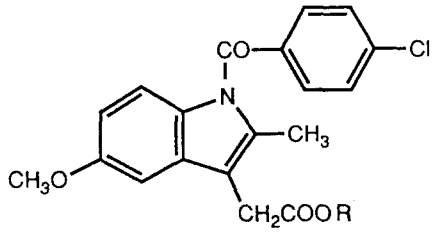

Fig. 1. R=H: Indomethacin, R=CH_2COOH: Acemetacin.

3.2 mm, while the vertical one set at 4 mm. Intensities of three reflections, (−2 −3 3), (3 1 −4), (−1 −2 −4), were repeatedly monitored every 1 hour during the data collection, and did not show any significant variations. All the reflections were corrected for usual Lorentz and polarization effects, but no absorption corrections were made. Of all 3550 independent reflections, 590 reflections which had $F \leq 3\sigma(F)$ were treated as unobserved. The space group was assigned as $P\bar{1}$ by zero moment statistics, and confirmed by subsequent structure determination procedure.

The structure was solved by the multisolution tangent formular refinement method. 816 reflections ($E \geq 1.2$) were used for phase generation, and the E-map revealed all the non-hydrogen atoms. But an unexpected peak, which was absent from acemetacin molecule, was found near to the acetoacetate group. It was separated by at least 2.4 Å from other atoms, and the integrated value of the electron density over an assumed volume for this peak amounted about to an oxygen atom. So it was supposed to be water (solvent) molecule which was co-crystallized during evaporation procedure, and the peak was assigned as an oxygen atom in the subsequent work.

The initial R value was 0.213. The structure was refined first isotropically to the R value of 0.158 by full matrix least squares procedure. Successive refinements with anisotropic temperature factors reduced the R value to 0.073. Difference Fourier synthesis calculated at this stage revealed all the hydrogen atoms of acemetacin and water molecule. Further refinements including hydrogen atoms converged the R value to 0.037

Table I. Crystal data

$C_{21}H_{18}NO_6Cl \cdot H_2O$	M.W. 443.91
1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid carboxymethyl ester	
Colorless transparent prism	Triclinic
$a=7.796(1)$ Å	$\alpha=97.35(1)°$
$b=10.245(2)$ Å	$\beta=96.34(1)°$
$c=13.542(3)$ Å	$\gamma=107.06(1)°$
Vol. of unit cell: 1012.9(3) Å^3	
$Dx=1.422$ g/cm^3	$Dm=1.42$ g/cm^3
Space group: $P\bar{1}$	$Z=2$
$F(000)=442.00$	$\mu(MoK\alpha)=2.36$ cm^{-1}

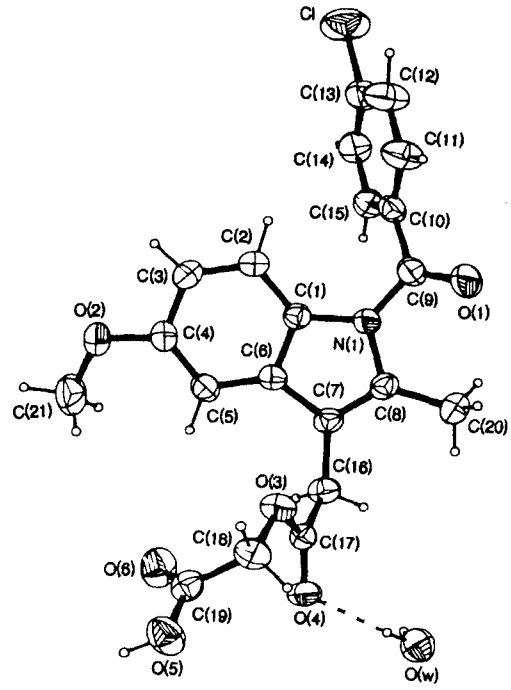

Fig. 2. The molecular structure of acemetacin. The thermal ellipsoids are drawn at the 50% probability level.

and wR ($[\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2}$) to 0.056 for 2960 reflections with $F \geq 3\sigma$ (F). In the final cycle, the maximum shift/e.s.d. ratio was 0.01. All the calculations were performed on a micro VAX 3100 computer using MolEN software package (Fair *et al.*, 1990). The atomic scattering factors were taken from "*International Tables for X-ray Crystallography*" (The International Union of Crystallography, 1974).

RESULTS AND DISCUSSION

The final atomic coordinates and temperature factors are listed in Table II and III. The observed and calculated structure factors are available upon request.

The structure of the molecule drawn by *ORTEP* (Johnson, 1975) is shown in Fig. 2 together with the atomic numbering system. The bonding distances and angles are presented in Table IV and Table V. All of the molecular dimensions are in the reasonable range compared to those of other related compounds (Kim *et al.*, 1986-1990; Kistenmacher and Marsh, 1972; Koo *et al.*, 1985; Foulon *et al.*, 1979).

The steric hindrance between the p-chlorophenyl and indole, and that between the methyl substituent of C(20) and carbonyl oxygen of O(1) prevent the carbonyl group C(9)-O(1) from being coplanar with the indole ring, thus reducing the double-bond character in N-C(9) bond. The same situations were observed in the case of indomethacin (Kistenmacher and Marsh, 1972). The methoxy group shows a tendency to be

Table II. Fractional coordinates ($\times 10^4$) and thermal parameters ($\times 10^3$) of non-hydrogen atoms with their e.s.d.'s in parentheses. The anisotropic temperature factors are in the form of $exp[-2\pi^2 (U_{11}a^{*2}h^2+U_{22}b^{*2}k^2+U_{33}c^{*2}l^2+2U_{12}a^*b^*hk+2U_{13}a^*c^*hl+2U_{23}b^*c^*kl)]$

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Acemetacin molecule									
C(1)	6776(2)	4624(1)	7212(1)	33(1)	35(1)	30(1)	11(0)	4(1)	5(1)
C(2)	7338(2)	3823(2)	6486(1)	41(1)	41(1)	42(1)	8(1)	5(1)	−6(1)
C(3)	9072(2)	4330(2)	6281(1)	45(1)	52(1)	45(1)	18(1)	10(1)	−5(1)
C(4)	10252(2)	5611(2)	6786(1)	34(1)	49(1)	46(1)	12(1)	10(1)	6(1)
C(5)	9736(2)	6385(2)	7534(1)	34(1)	37(1)	41(1)	8(1)	3(1)	4(1)
C(6)	7965(2)	5876(1)	7754(1)	34(1)	33(1)	30(1)	11(0)	2(1)	6(1)
C(7)	7033(2)	6395(1)	8494(1)	36(1)	37(1)	28(1)	12(1)	0(1)	2(1)
C(8)	5345(2)	5481(2)	8406(1)	38(1)	42(1)	27(1)	14(1)	5(1)	4(1)
C(9)	3588(2)	3217(2)	7340(1)	36(1)	41(1)	37(1)	5(1)	5(1)	7(1)
C(10)	3201(2)	2497(2)	6275(1)	30(1)	41(1)	36(1)	3(1)	0(1)	4(1)
C(11)	2746(3)	1071(2)	6081(1)	75(1)	42(1)	43(1)	1(1)	−1(1)	8(1)
C(12)	2345(4)	375(2)	5100(2)	96(1)	40(1)	52(1)	1(1)	3(1)	−1(1)
C(13)	2345(3)	1109(2)	4320(1)	51(1)	60(1)	40(1)	6(1)	2(1)	−2(1)
C(14)	2738(2)	2525(2)	4495(1)	49(1)	59(1)	37(1)	15(1)	2(1)	10(1)
C(15)	3185(2)	3217(2)	5478(1)	43(1)	42(1)	42(1)	12(1)	5(1)	8(1)
C(16)	7771(2)	7761(2)	9189(1)	45(1)	38(1)	39(1)	16(1)	1(1)	−1(1)
C(17)	9143(2)	7877(2)	10094(1)	35(1)	34(1)	32(1)	6(1)	8(1)	3(1)
C(18)	11135(2)	6920(2)	10928(1)	47(1)	46(1)	41(1)	13(1)	−3(1)	10(1)
C(19)	12869(2)	8001(2)	10846(1)	45(1)	44(1)	41(1)	21(1)	6(1)	7(1)
C(20)	3830(2)	5582(2)	8964(1)	45(1)	60(1)	46(1)	15(1)	14(1)	−1(1)
C(21)	13044(3)	7369(2)	6787(2)	57(1)	63(1)	107(2)	4(1)	40(1)	9(1)
CL	1790(1)	236(1)	3085(0)	122(1)	85(0)	42(0)	9(0)	5(0)	−15(0)
O(1)	2594(2)	2831(1)	7938(1)	55(1)	61(1)	47(1)	−5(1)	19(1)	5(1)
O(2)	11936(2)	5977(1)	6492(1)	41(1)	60(1)	77(1)	8(1)	26(1)	−5(1)
O(3)	9753(2)	6783(1)	10090(1)	48(1)	38(1)	40(1)	13(0)	−4(1)	0(1)
O(4)	9684(2)	8870(1)	10756(1)	51(1)	41(1)	36(1)	10(0)	3(1)	−5(1)
O(5)	14056(2)	8272(1)	11662(1)	46(1)	72(1)	52(1)	8(1)	−5(1)	17(1)
O(6)	13148(2)	8513(1)	10103(1)	58(1)	78(1)	50(1)	18(1)	14(1)	26(1)
N(1)	5123(2)	4383(1)	7608(1)	33(1)	36(1)	30(1)	6(0)	4(0)	2(0)
Water									
O(w)	7117(2)	10036(1)	11471(1)	51(1)	57(1)	55(1)	19(0)	6(1)	10(1)

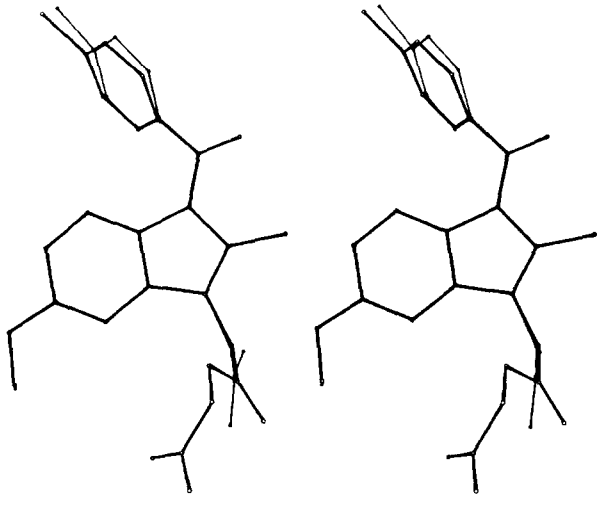

Fig. 3. The superimposed stereoview of acemetacin (heavy line) and indomethacin (light line) according to the procedure of Nyburg.

coplanar with the plane of indole ring due to the effective overlapping of remaining orbitals of oxygen with the π electron system of the ring. So the bond length of C(4)-O(2) is somewhat shortened compared to that of O(2)-C(21). Similiar effects are observed in the case of related compounds which have methoxy-aryl moiety (Kim *et al.*, 1987; 1989; 1990; Kistenmacher and Marsh, 1972). The carboxy group (in acetoacetoxy moiety) is somewhat perpendicular to the indole ring and this seems to be a common feature of arylacetate analogues (Kim *et al.*, 1986-1990; Kistenmacher and Marsh, 1972; Koo *et al.*, 1985; Foulon *et al.*, 1979). The p-chlorophenyl group is planar, but the indole ring is slightly distorted with the maximum deviation of 0.038 Å. The equations of least-squares planes of indole, p-chlorophenyl rings and the deviations of individual atoms from these planes are listed in the Table VI. The dihedral angle between the planes is 69.3°. The torsion angles around all bonds are shown in Table

VII. The compound is a derivative of indomethacin, and the conformation of the title compound is found to be quite similar to that of indomethacin (Kistenmacher and Marsh, 1972). The superimposed stereoview of the two compounds according to the procedure of Nyburg (Nyburg, 1974) was shown in Fig. 3. The largest differences were observed at the chlorine atoms of p-chlorophenyl (0.49 Å), and at the oxygens of (aceto)acetate group (0.92 Å).

The stereoscopic molecular packing is presented in Fig. 4. There are water molecules, which were co-crystallized during evaporation, with the ratio of one water per compound molecule in the crystal. The molecules are stabilized by three O-H···O type hydrogen

Table III. Fractional coordinates and thermal parameters (× 103) of hydrogen atoms with their e.s.d.'s in parentheses. The isotropic temperature factors are in the form of $exp(-8\pi^2 U \sin^2 u/\lambda^2)$

Atom	Bonded to	x/a	y/b	z/c	U
Acemetacin molecule					
H(2)	C(2)	661(2)	290(2)	614(1)	52(5)
H(3)	C(3)	959(2)	385(2)	582(1)	52(5)
H(5)	C(5)	1053(2)	726(2)	789(1)	39(4)
H(11)	C(11)	271(3)	59(2)	666(2)	75(6)
H(12)	C(12)	207(3)	−69(2)	491(2)	87(8)
H(14)	C(14)	271(2)	303(2)	393(1)	58(5)
H(15)	C(15)	348(2)	417(2)	561(1)	47(5)
H(161)	C(16)	835(2)	848(2)	885(1)	46(5)
H(162)	C(16)	687(3)	806(2)	944(2)	62(5)
H(181)	C(18)	1135(2)	599(2)	1089(1)	58(5)
H(182)	C(18)	1072(2)	715(2)	1155(1)	51(5)
H(201)	C(20)	272(3)	540(2)	852(2)	70(6)
H(202)	C(20)	420(3)	642(2)	940(2)	87(8)
H(203)	C(20)	358(3)	495(2)	939(2)	82(8)
H(211)	C(21)	1232(4)	803(3)	667(2)	103(9)
H(212)	C(21)	1416(3)	741(2)	650(2)	90(8)
H(213)	C(21)	1343(4)	757(3)	752(2)	129(11)
H(500)	O(5)	1514(4)	887(3)	1158(2)	118(10)
Water					
H(w1)	O(w)	703(3)	1045(2)	1092(2)	98(9)
H(w2)	O(w)	789(3)	964(2)	1133(2)	91(8)

Table IV. Bond distances in Angstroms with their estimated standard deviations in parentheses

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
C(1)	C(2)	1.390(2)	C(10)	C(11)	1.381(2)
C(1)	C(6)	1.398(2)	C(10)	C(15)	1.383(3)
C(1)	N(1)	1.417(2)	C(11)	C(12)	1.380(3)
C(2)	C(3)	1.372(2)	C(12)	C(13)	1.374(3)
C(3)	C(4)	1.399(2)	C(13)	Cl	1.735(2)
C(4)	C(5)	1.375(2)	C(13)	C(14)	1.374(3)
C(4)	O(2)	1.374(2)	C(14)	C(15)	1.380(2)
C(5)	C(6)	1.405(2)	C(16)	C(17)	1.504(2)
C(6)	C(7)	1.438(2)	C(17)	O(3)	1.339(2)
C(7)	C(8)	1.355(2)	C(17)	O(4)	1.203(2)
C(7)	C(16)	1.498(2)	C(18)	O(3)	1.438(2)
C(8)	C(20)	1.491(3)	C(18)	C(19)	1.501(2)
C(8)	N(1)	1.413(2)	C(19)	O(5)	1.303(2)
C(9)	C(10)	1.489(2)	C(19)	O(6)	1.205(2)
C(9)	N(1)	1.395(2)	C(21)	O(2)	1.412(2)
C(9)	O(1)	1.205(2)			

Table V. Bond angles in degrees with their standard deviations in parentheses

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C(2)	C(1)	C(6)	121.2(1)	C(9)	C(10)	C(15)	121.5(1)
C(2)	C(1)	N(1)	131.6(1)	C(11)	C(10)	C(15)	119.4(2)
C(6)	C(1)	N(1)	107.1(1)	C(10)	C(11)	C(12)	120.3(2)
C(1)	C(2)	C(3)	118.0(1)	C(11)	C(12)	C(13)	119.4(2)
C(2)	C(3)	C(4)	121.5(2)	C(12)	C(13)	C(14)	121.3(2)
C(3)	C(4)	C(5)	121.1(2)	C(12)	C(13)	Cl	119.7(2)
C(3)	C(4)	O(2)	114.5(2)	C(14)	C(13)	Cl	119.0(2)
C(5)	C(4)	O(2)	124.5(1)	C(13)	C(14)	C(15)	118.9(2)
C(4)	C(5)	C(6)	118.0(1)	C(10)	C(15)	C(14)	120.7(2)
C(1)	C(6)	C(5)	120.2(1)	C(7)	C(16)	C(17)	117.9(2)
C(1)	C(6)	C(7)	107.8(1)	C(16)	C(17)	O(3)	113.9(1)
C(5)	C(6)	C(7)	132.0(1)	C(16)	C(17)	O(4)	123.6(2)
C(6)	C(7)	C(8)	108.2(1)	O(3)	C(17)	O(4)	122.5(1)
C(6)	C(7)	C(16)	125.4(1)	C(19)	C(18)	O(3)	110.8(1)
C(8)	C(7)	C(16)	126.3(2)	C(18)	C(19)	O(5)	111.6(2)
C(7)	C(8)	C(20)	128.9(1)	C(18)	C(19)	O(6)	123.9(1)
C(7)	C(8)	N(1)	109.0(1)	O(5)	C(19)	O(6)	124.4(1)
C(20)	C(8)	N(1)	122.0(1)	C(4)	O(2)	C(21)	117.6(2)
C(10)	C(9)	N(1)	117.0(1)	C(17)	O(3)	C(18)	114.1(1)
C(10)	C(9)	O(1)	121.5(1)	C(1)	N(1)	C(8)	108.0(1)
N(1)	C(9)	O(1)	121.5(1)	C(1)	N(1)	C(9)	127.2(1)
C(9)	C(10)	C(11)	119.0(2)	C(8)	N(1)	C(9)	124.6(1)

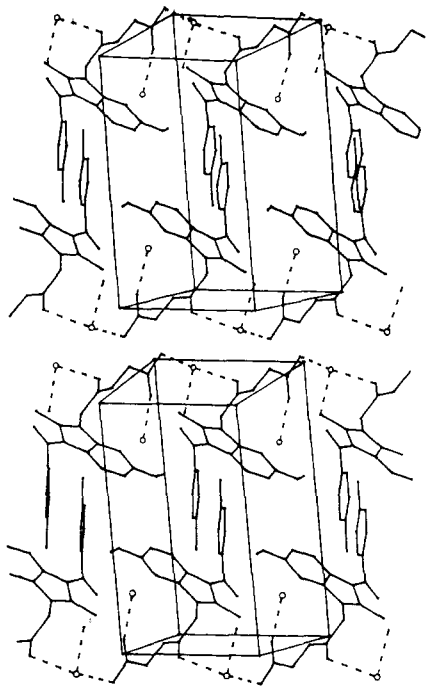

Fig. 4. The stereoscopic packing diagram for acemetacin. The broken lines indicate O-H···O type hydrogen bonds.

bonds between the oxygens of the acetoacetate of the compound and the water molecule in the crystal. The distance between the oxygens of O(4)···H(w2)-O

Table VI. The equations of the least-squares planes of the planar regions of the compound, and the deviations of individual atoms from these planes (Å).

Equations: Plane A (Indole ring)
$0.4246X-0.6018Y+0.6764Z=5.9642$
Plane B (Phenyl ring)
$0.9952X+0.0967Y-0.0161Z=0.7570$

Deviations from:					
Atom	Plane A	Atom	Plane A	Atom	Plane B
C(1)	0.038*	C(10)	0.606	C(10)	−0.010*
C(2)	−0.018*	C(16)	0.040	C(11)	0.014*
C(3)	−0.029*	C(17)	−1.210	C(12)	−0.006*
C(4)	0.009*	C(20)	−0.001	C(13)	−0.006*
C(5)	0.009*	C(21)	0.344	C(14)	0.013*
C(6)	0.017*	O(1)	−0.568	C(15)	−0.004*
C(7)	−0.021*	O(2)	−0.001	C(9)	0.042
C(8)	−0.032*			O(1)	0.848
N	0.029*			N	−0.860
C(9)	−0.040			Cl	0.009

*Atoms used for the calculation of the equation.

Table VII. Torsion angles

Atom 1	Atom 2	Atom 3	Atom 4	Angle	Atom 1	Atom 2	Atom 3	Atom 4	Angle
C(21)	O(2)	C(4)	C(3)	165.7(2)	C(21)	O(2)	C(4)	C(5)	−16.6(3)
C(18)	O(3)	C(17)	O(4)	−1.5(2)	C(18)	O(3)	C(17)	C(16)	176.9(1)
C(17)	O(3)	C(18)	C(19)	−69.3(2)	C(8)	N(1)	C(1)	C(2)	174.1(2)
C(8)	N(1)	C(1)	C(6)	−1.4(2)	C(9)	N(1)	C(1)	C(2)	−0.2(3)
C(9)	N(1)	C(1)	C(6)	−175.7(1)	C(1)	N(1)	C(8)	C(7)	1.8(2)
C(1)	N(1)	C(8)	C(20)	177.4(1)	C(9)	N(1)	C(8)	C(7)	176.3(1)
C(9)	N(1)	C(8)	C(20)	−8.1(2)	C(1)	N(1)	C(9)	O(1)	149.3(2)
C(1)	N(1)	C(9)	C(10)	32.5(2)	C(8)	N(1)	C(9)	O(1)	−24.1(2)
C(8)	N(1)	C(9)	C(10)	154.2(1)	N(1)	C(1)	C(2)	C(3)	−178.2(2)
C(6)	C(1)	C(2)	C(3)	−3.2(2)	N(1)	C(1)	C(6)	C(5)	−179.5(1)
N(1)	C(1)	C(6)	C(7)	0.6(2)	C(2)	C(1)	C(6)	C(5)	3.4(2)
C(2)	C(1)	C(6)	C(7)	−175.5(1)	C(1)	C(2)	C(3)	C(4)	0.3(3)
C(2)	C(3)	C(4)	O(2)	−179.7(2)	C(2)	C(3)	C(4)	C(5)	2.4(3)
O(2)	C(4)	C(5)	C(6)	−179.9(1)	C(3)	C(4)	C(5)	C(6)	−2.2(2)
C(4)	C(5)	C(6)	C(1)	−0.6(2)	C(4)	C(5)	C(6)	C(7)	−177.9(2)
C(1)	C(6)	C(7)	C(8)	0.5(2)	C(1)	C(6)	C(7)	C(16)	−175.7(1)
C(5)	C(6)	C(7)	C(8)	−178.2(2)	C(5)	C(6)	C(7)	C(16)	5.7(3)
C(6)	C(7)	C(8)	N(1)	−1.4(2)	C(6)	C(7)	C(8)	C(20)	−176.6(2)
C(16)	C(7)	C(8)	N(1)	174.7(1)	C(16)	C(7)	C(8)	C(20)	−0.6(3)
C(6)	C(7)	C(16)	C(17)	−77.8(2)	C(8)	C(7)	C(16)	C(17)	106.8(2)
O(1)	C(9)	C(10)	C(11)	−47.6(3)	O(1)	C(9)	C(10)	C(15)	128.6(2)
N(1)	C(9)	C(10)	C(11)	134.2(2)	N(1)	C(9)	C(10)	C(15)	−49.6(2)
C(9)	C(10)	C(11)	C(12)	178.7(2)	C(15)	C(10)	C(11)	C(12)	2.4(3)
C(9)	C(10)	C(15)	C(14)	−176.8(2)	C(11)	C(10)	C(15)	C(14)	−0.7(3)
C(10)	C(11)	C(12)	C(13)	−2.2(4)	C(11)	C(12)	C(13)	CL	−178.5(2)
C(11)	C(12)	C(13)	C(14)	0.1(4)	CL	C(13)	C(14)	C(15)	−179.8(2)
C(12)	C(13)	C(14)	C(15)	1.6(3)	C(13)	C(14)	C(15)	C(10)	−1.4(3)
C(7)	C(16)	C(17)	O(3)	9.6(2)	C(7)	C(16)	C(17)	O(4)	−172.0(2)
O(3)	C(18)	C(19)	O(5)	171.4(1)	O(3)	C(18)	C(19)	O(6)	−11.2(2)

(w) is 2.812 Å (hydrogen bond angle: 168.7°); the distance of O(5)-H(500)···O(w) of a neighboring molecule at (x+1, y, z) is 2.598 Å (bond angle: 177.4 Å); the distance between O(6)···H(w1)-O(w) of the water molecule at (2-x, 2-y, 2-z) is 2.774 Å (bond angle: 173.0°). The other interatomic contacts are normal *van der Waals'* forces.

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