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The Crystal and Molecular Structure of Pikromycin

Akio Furusaki,* Takeshi Matsumoto, Kimio Furuhata,† and Haruo Ogura†
Department of Chemistry, Faculty of Science, Hokkaido University, Kita-ku, Sapporo 060
† *School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108*

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The detailed molecular geometry of pikromycin ($C_{28}H_{47}NO_8$) has been examined by means of X-ray crystal analysis. The crystals are orthorhombic, with four molecules in a unit cell with dimensions of $a=11.295$, $b=25.734$, and $c=10.509$ Å; the space group is $P2_12_12_1$. 2259 unique intensity data were collected on a four-circle diffractometer with graphite-monochromated Cu $K\alpha$ radiation. The structure was solved by the Monte Carlo direct method, using the 30 strongest reflections as the starting set; the 215th random phase set led to the correct solution. The R value reached 0.056 by block-diagonal least-squares refinements. The conformation of the fourteen-membered macrolide ring is considerably different from that of (*p*-bromobenzoyl)pikromycin in the solid state; *e.g.*, the C=C and C=O conjugated double bonds are cisoid in pikromycin, while they are transoid in the derivative. The molecules are held together through two kinds of intermolecular hydrogen bonds, forming a three-dimensional hydrogen-bonded structure.

Pikromycin (**1a**) is an antibiotic isolated from *Streptomyces flavochromogenese*, and is active against gram-positive bacteria.[1)] The structure of **1a** was determined as **1b** by chemical and spectroscopic studies,[2)] and by an X-ray study of kromycin.[3)] An X-ray analysis of (*p*-bromobenzoyl)pikromycin (**2**) further revealed that the conformation of the fourteen-membered macrolide ring resembles the "diamond" conformation model (diamond model D) shown in Fig. 1.[4)] It was later suggested from NMR and CD experiments that the macro-ring conformation of **1a** in the solid state might differ from this conformation of **2**.[5)] Therefore, in order to obtain exact and detailed information about the molecular conformation of **1a** itself, we have now undertaken an X-ray crystal analysis.

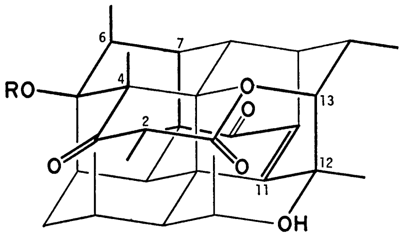
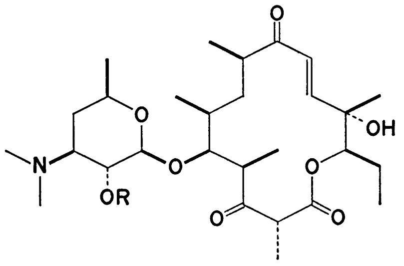


Fig. 1. Diamond model D applied to (*p*-bromobenzoyl)-pikromycin. The thick lines denote the bonds in the molecule.



Ib: R = H

2 : R = p-BrC_6H_4CO

Experimental

Colorless single crystals of **1a** were grown from a methanol solution. The sample used for the X-ray measurement had dimensions of about 0.2×0.2×0.4 mm³. The crystal data are summarized in Table 1. The cell dimensions and diffraction intensities were measured on a Rigaku automatic, four-circle diffractometer with graphite-monochromated Cu $K\alpha$ radiation ($\lambda=1.5418$ Å). The θ-2θ continuous-scan technique was applied at a θ scan rate of 2° min^{-1}; the background was measured for 10 s at each end of the scan range. Three standard reflections, measured at intervals of every 50 reflections, showed no significant decrease in intensity during the course of data collection. The intensities were corrected for the Lorentz and polarization factors, but not for the absorption or the extinction effect. In the range of 2θ values up to 125°, 2259 independent structure factors above the $\sigma(F)$ level were selected for the structure determination.

Structure Determination

Since it had already been reported that an attempt to solve the present structure with the MULTAN program[6)] had been unsuccessful,[4)] we tried the Monte Carlo direct method.[7)] The 30 strongest reflections were chosen as the starting set. In order to extend the tentative-phase set derived from random numbers, 15 cycles of the tangent procedure were performed using 520 $|E|$ values above 1.30. As the 215th phase set showed a low R_K value of 0.297 ($R_K=\Sigma||E_o|-k|E_c||/\Sigma|E_o|$), 6 additional cycles of the tangent procedure were carried out using 617 $|E|$ values above 1.20; the R_K value thereupon dropped to 0.280. An E-map based on 586 phases revealed the locations of all the 37 non-hydrogen atoms.

The structure thus obtained was refined by the block-diagonal least-squares method with anisotropic

Table 1. The crystal data

$C_{28}H_{47}NO_8$	Mol wt 525.68
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Cell dimensions	$a=11.295(1)$ Å
	$b=25.734(3)$ Å
	$c=10.509(1)$ Å
V	3054.6 Å³
Z	4
D_c	1.143 g cm^{-3}
μ(Cu $K\alpha$)	6.41 cm^{-1}

Table 2. The final atomic parameters and estimated standard deviations
The atomic coordinates are multiplied by 10^4.

Atom	x	y	z	$B_{eq}{}^{a)}/\text{Å}^2$	Atom	x	y	z	$B_{eq}{}^{a)}/\text{Å}^2$
O(1)	2395(2)	2282(1)	3195(2)	3.13	C(11)	2747(4)	1845(1)	5718(4)	3.36
O(2)	4152(2)	2623(1)	3717(3)	4.93	C(12)	2207(3)	1553(1)	4613(4)	3.01
O(3)	3464(2)	3859(1)	4186(3)	3.97	C(13)	2780(3)	1745(1)	3376(4)	2.89
O(4)	668(2)	4056(1)	6659(2)	2.95	C(14)	2399(4)	1459(1)	2165(4)	3.52
O(5)	3914(3)	2288(1)	7802(3)	6.64	C(15)	3276(4)	1553(2)	1067(5)	5.08
O(6)	2605(2)	1021(1)	4734(2)	3.62	C(16)	3285(5)	3392(2)	1791(4)	6.33
O(7)	907(2)	4401(1)	8643(3)	3.50	C(17)	644(4)	3954(2)	4015(4)	4.07
O(8)	−867(3)	4869(1)	5954(3)	4.97	C(18)	3347(4)	3824(2)	7875(4)	4.51
N	−1903(3)	5485(1)	8041(3)	3.37	C(19)	1237(5)	2439(2)	9231(4)	5.85
C(1)	3162(4)	2669(1)	3354(4)	3.13	C(20)	874(4)	1575(2)	4577(4)	4.19
C(2)	2574(4)	3183(1)	2953(4)	3.19	C(21)	652(3)	4525(1)	7335(4)	2.79
C(3)	2615(4)	3577(1)	4033(4)	2.89	C(22)	−599(4)	4744(1)	7231(4)	3.22
C(4)	1505(3)	3636(1)	4843(4)	2.63	C(23)	−714(4)	5236(1)	8045(4)	2.88
C(5)	1785(3)	3898(1)	6113(4)	2.96	C(24)	−349(4)	5093(2)	9416(4)	3.56
C(6)	2485(4)	3525(1)	7012(4)	3.47	C(25)	881(4)	4857(1)	9434(4)	3.74
C(7)	1613(4)	3192(2)	7788(4)	3.71	C(26)	1227(5)	4669(2)	10758(4)	6.08
C(8)	2179(4)	2735(2)	8508(4)	3.87	C(27)	−2887(4)	5117(2)	8086(4)	4.60
C(9)	2867(4)	2380(2)	7635(4)	4.48	C(28)	−2043(4)	5850(2)	6975(4)	5.39
C(10)	2211(4)	2137(1)	6542(4)	3.68					

a) $B_{eq}=8\pi^2(u_1{}^2+u_2{}^2+u_3{}^2)/3$, where u_i is the root-mean-square deviation in the ith principal axis of the thermal ellipsoid.

temperature factors. After all the 47 hydrogen atoms had been located in a difference Fourier map, further least-squares refinements were repeated including the hydrogen atoms with isotropic temperature factors. In this refinement, the following weighting scheme was used:

$$w = 1/\{\sigma(F)^2 \exp(AX^2+BY^2+CXY+DX+EY)\},$$

where $X=|F_o|$ and $Y=\sin\theta/\lambda$. The A, B, C, D, and E coefficients are constants which were determined from the $(\Delta F)^2$ values; $A=0.3052\times10^{-4}$, $B=-5.563$, $C=0.04688$, $D=-0.01148$, and $E=2.250$. The final R value was 0.056. The final atomic parameters are listed in Table 2. The tables of the anisotropic thermal parameters and hydrogen parameters, and the F_o-F_c table are kept at the Chemical Society of Japan (Document No. 8204).

The calculations were done on a HITAC M-200H computer at the Hokkaido University Computing Center, using our own programs. The atomic scattering factors were taken from the International Tables.[8]

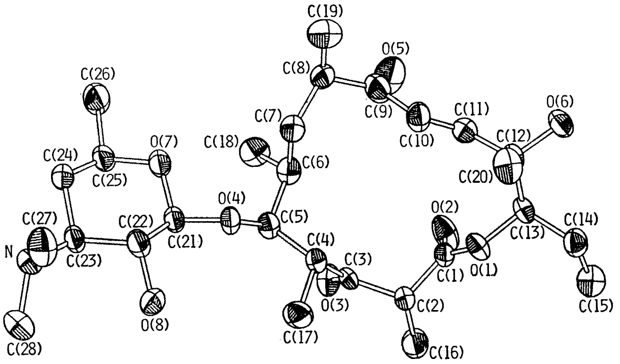


Fig. 2. A perspective view of the pikromycin molecule. Each non-hydrogen atom is represented as a thermal ellipsoid enclosing a 50% probability.

Results and Discussion

Molecular Structure. The molecular skeleton of **1a** obtained is illustrated in Fig. 2; it corresponds exactly to the **1b** structure. The bond distances and angles and the torsion angles are given in Tables 3 and 4 respectively.

As will be seen from Figs. 1 and 2, the macro-ring conformation of **1a** is considerably different from that of **2**; *e.g.*, very great differences of 159, 143, and 176° can be seen for the torsion angles about the C(5)–C(6), C(8)–C(9), and C(9)–C(10) bonds respectively. Of these, the difference for the last bond corresponds to the fact that, while the C(10)=C(11) and C(9)=O(5) conjugated double bonds are transoid for **2**, they are cisoid for **1a**. Notwithstanding the incorporation in the macrolide ring, the ester part keeps the geometry characteristic of secondary alcohol esters, *i.e.*, the synperiplanar configuration of the C(13)–O(1)–C(1)–O(2) part and the eclipsed conformation of the H–C(13)–O(1)–C(1) part.

When the macro ring is viewed along the normal of its mean plane, it looks like a somewhat-deformed right trapezoid with the four corners at the C(2), C(5), C(8), and C(12) atoms (see Fig. 2). For the cisoid configuration of the C(10)=C(11) and C(9)=O(5) bonds, the C(8)–C(9)–C(10)–C(11)–C(12) zigzag chain can form one side of such a polygon. Since the torsion angles about the C(4)–C(5), C(5)–C(6), C(7)–C(8), and C(8)–C(9) bonds do not much deviate from −60°, the C(5)–C(6)–C(7)–C(8) side makes nearly right angles with the C(2)–C(3)–C(4)–C(5) and

Table 3. The bond distances (l/Å) and angles (ϕ/°), with their standard deviations
The standard deviations given in parentheses refer to the last decimal position.

C(1)-C(2)	1.541(5)	C(23)-N	1.488(5)	C(10)-C(11)-C(12)	127.8(4)
C(1)-O(1)	1.328(4)	C(24)-C(25)	1.517(6)	C(11)-C(12)-C(13)	108.7(3)
C(1)-O(2)	1.187(5)	C(25)-C(26)	1.525(6)	C(11)-C(12)-C(20)	113.8(3)
C(2)-C(3)	1.522(5)	C(25)-O(7)	1.437(5)	C(11)-C(12)-O(6)	106.1(3)
C(2)-C(16)	1.558(6)	C(27)-N	1.460(5)	C(13)-C(12)-C(20)	112.8(3)
C(3)-C(4)	1.523(5)	C(28)-N	1.472(5)	C(13)-C(12)-O(6)	104.3(3)
C(3)-O(3)	1.212(5)	C(2)-C(1)-O(1)	109.2(3)	C(20)-C(12)-O(6)	110.5(3)
C(4)-C(5)	1.529(5)	C(2)-C(1)-O(2)	125.3(3)	C(12)-C(13)-C(14)	115.5(3)
C(4)-C(17)	1.540(6)	O(1)-C(1)-O(2)	125.5(3)	C(12)-C(13)-O(1)	106.8(3)
C(5)-C(6)	1.562(5)	C(1)-C(2)-C(3)	110.9(3)	C(14)-C(13)-O(1)	105.3(3)
C(5)-O(4)	1.443(5)	C(1)-C(2)-C(16)	106.8(3)	C(13)-C(14)-C(15)	111.5(3)
C(6)-C(7)	1.540(6)	C(3)-C(2)-C(16)	109.8(3)	C(22)-C(21)-O(4)	107.1(3)
C(6)-C(18)	1.537(6)	C(2)-C(3)-C(4)	117.2(3)	C(22)-C(21)-O(7)	109.6(3)
C(7)-C(8)	1.537(6)	C(2)-C(3)-O(3)	121.3(4)	O(4)-C(21)-O(7)	106.9(3)
C(8)-C(9)	1.510(6)	C(4)-C(3)-O(3)	121.3(3)	C(21)-C(22)-C(23)	110.1(3)
C(8)-C(19)	1.514(6)	C(3)-C(4)-C(5)	111.2(3)	C(21)-C(22)-O(8)	110.5(3)
C(9)-C(10)	1.503(6)	C(3)-C(4)-C(17)	104.8(3)	C(23)-C(22)-O(8)	108.9(3)
C(9)-O(5)	1.219(5)	C(5)-C(4)-C(17)	112.9(3)	C(22)-C(23)-C(24)	107.5(3)
C(10)-C(11)	1.298(6)	C(4)-C(5)-C(6)	111.2(3)	C(22)-C(23)-N	115.4(3)
C(11)-C(12)	1.512(6)	C(4)-C(5)-O(4)	106.9(3)	C(24)-C(23)-N	110.2(3)
C(12)-C(13)	1.534(6)	C(6)-C(5)-O(4)	112.1(3)	C(23)-C(24)-C(25)	110.6(3)
C(12)-C(20)	1.507(6)	C(5)-C(6)-C(7)	109.8(3)	C(24)-C(25)-C(26)	111.9(4)
C(12)-O(6)	1.445(4)	C(5)-C(6)-C(18)	111.8(3)	C(24)-C(25)-O(7)	109.8(3)
C(13)-C(14)	1.531(6)	C(7)-C(6)-C(18)	111.8(3)	C(26)-C(25)-O(7)	105.3(3)
C(13)-O(1)	1.463(4)	C(6)-C(7)-C(8)	114.9(4)	C(1)-O(1)-C(13)	119.9(3)
C(14)-C(15)	1.540(6)	C(7)-C(8)-C(9)	112.2(3)	C(5)-O(4)-C(21)	117.1(3)
C(21)-C(22)	1.525(5)	C(7)-C(8)-C(19)	109.9(4)	C(21)-O(7)-C(25)	111.5(3)
C(21)-O(4)	1.401(4)	C(9)-C(8)-C(19)	111.3(3)	C(23)-N-C(27)	114.2(3)
C(21)-O(7)	1.440(5)	C(8)-C(9)-C(10)	117.5(4)	C(23)-N-C(28)	111.9(3)
C(22)-C(23)	1.534(5)	C(8)-C(9)-O(5)	122.0(4)	C(27)-N-C(28)	110.9(3)
C(22)-O(8)	1.413(5)	C(10)-C(9)-O(5)	120.5(4)		
C(23)-C(24)	1.543(6)	C(9)-C(10)-C(11)	121.4(4)		

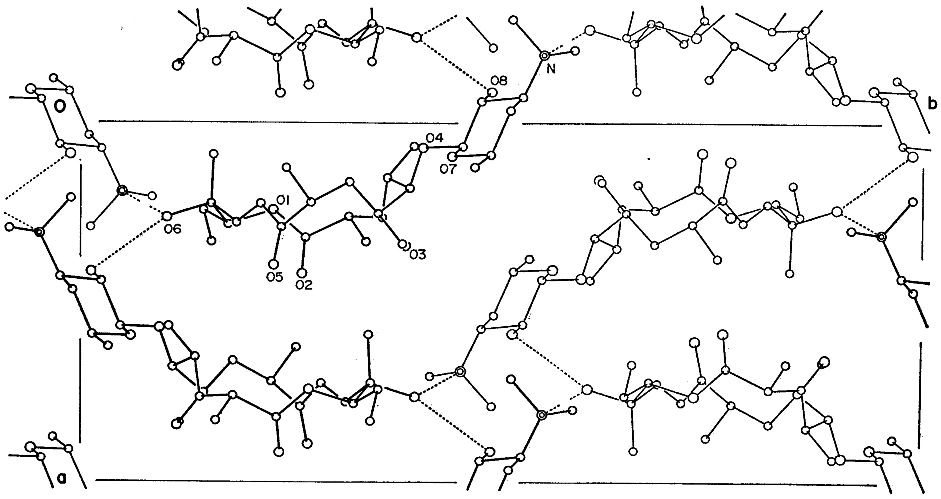


Fig. 3. The crystal structure viewed along the c axis.

C(8)-C(9)-C(10)-C(11)-C(12) sides; consequently, the latter two are nearly parallel. Because of the existence of the ester group having the special geometry mentioned above, the C(12)-C(13)-O(1)-C(1)-C(2) side deviates considerably from a straight line. The reason why the present macro ring does not take a rectangular form is probably that the planar ester part would occupy exactly one corner of the rectangle as long as the C(10)=C(11) and C(9)=O(5) bonds maintain the cisoid configuration.

The C(1)=O(2), C(3)=O(3), and C(9)=O(5) carbonyl groups protrude from the mean plane of the

Table 4. The torsion angles (ϕ/°)

O(1)-C(1)-C(2)-C(3)	124.1	C(10)-C(11)-C(12)-C(13)	120.4
O(1)-C(1)-C(2)-C(16)	−116.3	C(10)-C(11)-C(12)-C(20)	−6.2
O(2)-C(1)-C(2)-C(3)	−57.6	C(10)-C(11)-C(12)-O(6)	−127.9
O(2)-C(1)-C(2)-C(16)	62.0	C(11)-C(12)-C(13)-C(14)	175.6
C(2)-C(1)-O(1)-C(13)	173.3	C(11)-C(12)-C(13)-O(1)	−67.7
O(2)-C(1)-O(1)-C(13)	−5.0	C(20)-C(12)-C(13)-C(14)	−57.3
C(1)-C(2)-C(3)-C(4)	−98.6	C(20)-C(12)-C(13)-O(1)	59.5
C(1)-C(2)-C(3)-O(3)	86.5	O(6)-C(12)-C(13)-C(14)	62.7
C(16)-C(2)-C(3)-C(4)	143.7	O(6)-C(12)-C(13)-O(1)	179.4
C(16)-C(2)-C(3)-O(3)	−31.3	C(12)-C(13)-C(14)-C(15)	−162.2
C(2)-C(3)-C(4)-C(5)	161.4	O(1)-C(13)-C(14)-C(15)	80.3
C(2)-C(3)-C(4)-C(17)	−76.3	C(12)-C(13)-O(1)-C(1)	108.7
O(3)-C(3)-C(4)-C(5)	−23.6	C(14)-C(13)-O(1)-C(1)	−128.0
O(3)-C(3)-C(4)-C(17)	98.6	O(4)-C(21)-C(22)-C(23)	175.2
C(3)-C(4)-C(5)-C(6)	−71.9	O(4)-C(21)-C(22)-O(8)	−64.4
C(3)-C(4)-C(5)-O(4)	165.5	O(7)-C(21)-C(22)-C(23)	59.6
C(17)-C(4)-C(5)-C(6)	170.6	O(7)-C(21)-C(22)-O(8)	179.9
C(17)-C(4)-C(5)-O(4)	48.1	C(22)-C(21)-O(4)-C(5)	151.9
C(4)-C(5)-C(6)-C(7)	−87.5	O(7)-C(21)-O(4)-C(5)	−90.6
C(4)-C(5)-C(6)-C(18)	147.9	C(22)-C(21)-O(7)-C(25)	−62.7
O(4)-C(5)-C(6)-C(7)	32.0	O(4)-C(21)-O(7)-C(25)	−178.5
O(4)-C(5)-C(6)-C(18)	−92.6	C(21)-C(22)-C(23)-C(24)	−55.6
C(4)-C(5)-O(4)-C(21)	−144.0	C(21)-C(22)-C(23)-N	−179.1
C(6)-C(5)-O(4)-C(21)	94.1	O(8)-C(22)-C(23)-C(24)	−176.9
C(5)-C(6)-C(7)-C(8)	168.3	O(8)-C(22)-C(23)-N	59.6
C(18)-C(6)-C(7)-C(8)	−67.1	C(22)-C(23)-C(24)-C(25)	55.4
C(6)-C(7)-C(8)-C(9)	−55.8	N-C(23)-C(24)-C(25)	−178.0
C(6)-C(7)-C(8)-C(19)	180.0	C(22)-C(23)-N-C(27)	40.3
C(7)-C(8)-C(9)-C(10)	−57.8	C(22)-C(23)-N-C(28)	−86.7
C(7)-C(8)-C(9)-O(5)	122.7	C(24)-C(23)-N-C(27)	−81.7
C(19)-C(8)-C(9)-C(10)	65.7	C(24)-C(23)-N-C(28)	151.2
C(19)-C(8)-C(9)-O(5)	−113.8	C(23)-C(24)-C(25)-C(26)	−175.2
C(8)-C(9)-C(10)-C(11)	177.2	C(23)-C(24)-C(25)-O(7)	−58.6
O(5)-C(9)-C(10)-C(11)	−3.3	C(24)-C(25)-O(7)-C(21)	62.2
C(9)-C(10)-C(11)-C(12)	176.7	C(26)-C(25)-O(7)-C(21)	−177.2

macro ring to the same side, while the $C(20)H_3$ methyl group is axially placed on the opposite side of this plane. Each of the remaining seven groups attached to the macro ring is equatorially or isoclinally oriented outside the macro ring. The pyranose ring in the D-desosamine moiety has a chair form; all the four atomic groups on this ring occupy the equatorial positions.

Crystal Structure. The molecular arrangement viewed along the c axis is shown in Fig. 3. The macro rings are nearly parallel to the (100) plane, and are arranged on the two-fold screw axis penetrating them approximately perpendicularly. The crystal contains two kinds of intermolecular hydrogen bonds, O(6)–H···N′ and O(8)–H···O(6″); the O···N and O···O distances are 2.829(4) and 2.958(4) Å respectively.** The molecules are connected by these hydrogen bonds, forming a three-dimensional hydrogen-bonded structure.

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** The N′ and O(6″) positions are obtained from the N and O(6) coordinates by the symmetry operations, $(-x, -1/2+y, 3/2-z)$ and $(-1/2+x, 1/2-y, 1-z)$, respectively.