X-Ray Crystallographies of Leucomycin A_5 and Rokitamycin Monomethylacetal

KANAKO YAMASHITA and KENJI KINOSHITA*

Institute for Life Science Research,
Asahi Chemical Industry Co., Ltd.,
632-1, Mifuku, Ohito-cho, Shizuoka 410-23, Japan

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Leucomycin A_5 (**1**) is one of the components of a 16-membered macrolide antibiotic complex, leucomycin (kitasamycin), produced by *Streptomyces kitasatoensis*.[1,2] Rokitamycin (**2**) is a semi-synthetic drug with a propionyl group at 3″ position of leucomycin A_5 (**1**).[3] Leucomycin and rokitamycin (**2**) are now widely used as therapeutic agents for human and animals. Interestingly, rokitamycin (**2**) has a unique characteristic including antibacterial activities against the macrolide-resistant strains, *Staphylococcus aureus* 0116 and *Streptococcus pyogenes* 1022, and hardly induce resistance. The knowledge of the three-dimensional structures of leucomycin A_5 (**1**) and rokitamycin (**2**) should be important for research into the relationship between molecular stereostructure and antibacterial activity. In order to elucidate the stereochemistries of these molecules, X-ray diffraction studies were undertaken. From these studies, it was shown that rokitamycin (**2**) with MeOH when recrystallized from a mixture of MeOH-H_2O formed the hemiacetal derivative at the formyl moiety, rokitamycin monomethylacetal (**3**).[4] We here now report our study of the X-ray crystallography of leucomycin A_5 (**1**) and rokitamycin monomethylacetal (**3**).

Results and Discussion

Fig. 1 shows the ORTEP[5] views of molecular structures in leucomycin A_5 (**1**) and rokitamycin monomethylacetal (**3**). The absolute configuration of **1** and **3** are determined relative to that of the D-mycaminose and L-mycarose. These results show that the configurations at C-3, C-4, C-5, C-6, C-8, C-9 and C-15 in the aglycone of **1** and **3** are *R*, *S*, *S*, *R*, *R*, *R* and *R*, respectively. The configuration of monomethylacetal group in **3** is *S*.

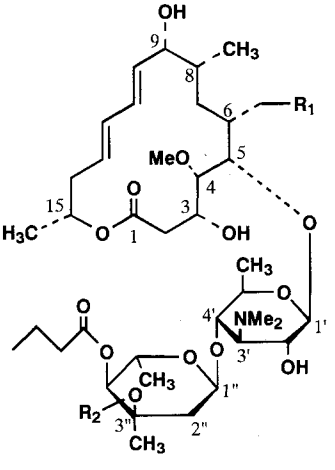
The comparison is made between the conformations in the crystalline states of 16-membered macrolides, **1** and **3** determined by X-ray crystallography. Table 1 shows torsion angles of the 16 bonds constituting the macrocyclic lactone ring and spatial arrangement between the macrolide ring and mycaminose, and between mycaminose and mycarose. The lactone rings in **1** and **3** have a very similar conformation each other. The presence of the 3″-propionyl group and hemiacetal moiety in **3** have very little effect on the conformation of the 16-membered lactone ring in comparison with **1**. Similarity is also found at spatial arrangement between the macrolide ring and mycaminose, and between the two sugars, mycaminose and mycarose.

Experimental

The cell parameters, data collection and refinement details for leucomycin A_5 (**1**) and rokitamycin monomethylacetal (**3**) are summarized in Table 2.

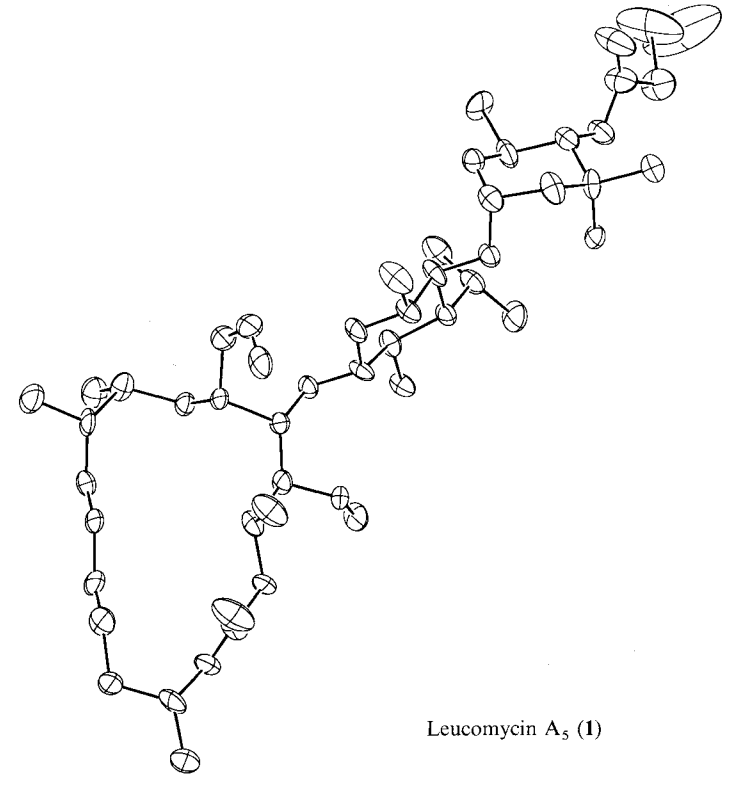
Single crystals of **1** and **3** were obtained as colorless blocks by recrystallization from 1,2-dichloroethane and a mixture of MeOH-H_2O, respectively. To prevent these crystals from decomposition due to vaporization of these labile solvents of crystallization, specimens used for the analysis were coated with the epoxy functionalized resins.

Data were collected for **1** and **3** using similar methods. A crystal was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated CuKα radiation ($\lambda = 1.54178$ Å). Cell parameters were determined

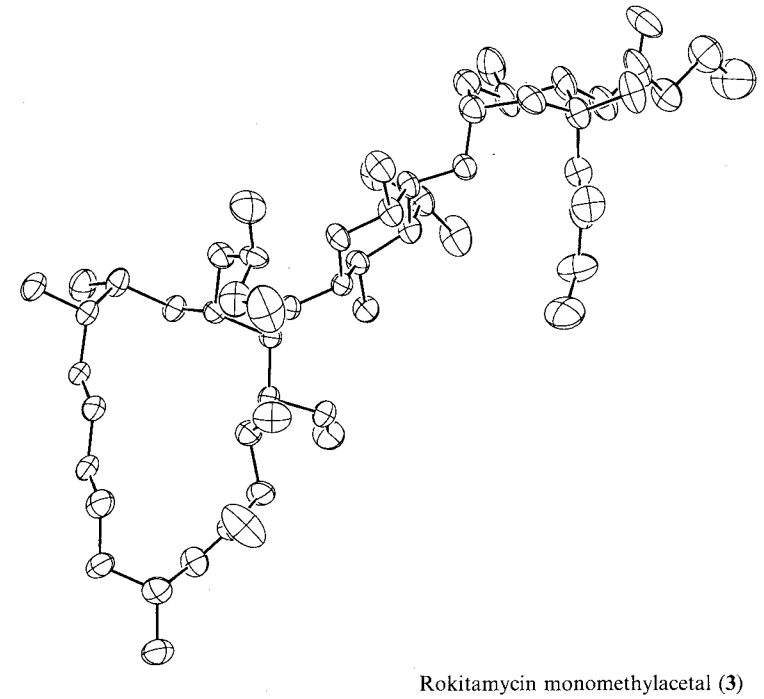


	R_1	R_2
Leucomycin A_5 (**1**)	CHO	H
Rokitamycin (**2**)	CHO	$COCH_2CH_3$
Rokitamycin monomethylacetal (**3**)	$CH(OH)OCH_3$	$COCH_2CH_3$

Fig. 1. The ORTEP view of leucomycin A_5 (**1**) and rokitamycin monomethylacetal (**3**).



Leucomycin A_5 (**1**)



Rokitamycin monomethylacetal (**3**)

and refined from 15 reflections in the range $56° < 2\theta < 60°$. Reflections were collected using the $\omega/2\theta$ scan technique to a maximum 2θ value of 120° at room temperature. The intensities were corrected for the Lorentz and polarization factors, but not for the extinction effect and the absorption.

The structure was solved by direct methods (using the SIR92[6] programs). Refinement was by full-matrix least-squares refinement calculations of F, initially with isotropic and finally with anisotropic thermal param-

Table 1. Torsion angles of leucomycin A_5 (**1**) and rokitamycin monomethylacetal (**3**).

Torsion	Torsion Angle[a] (degrees)	
	1	3
C (1)-C (2)-C (3)-C (4)	180	-171
C (2)-C (3)-C (4)-C (5)	-171	-166
C (3)-C (4)-C (5)-C (6)	-60	-60
C (4)-C (5)-C (6)-C (7)	-54	-70
C (5)-C (6)-C (7)-C (8)	175	-178
C (6)-C (7)-C (8)-C (9)	-60	-53
C (7)-C (8)-C (9)-C(10)	-63	-59
C (8)-C (9)-C(10)-C(11)	136	132
C (9)-C(10)-C(11)-C(12)	-179	-179
C(10)-C(11)-C(12)-C(13)	-179	-178
C(11)-C(12)-C(13)-C(14)	-171	-174
C(12)-C(13)-C(14)-C(15)	112	117
C(13)-C(14)-C(15)-O(16)	-61	-58
C(14)-C(15)-O(16)-C (1)	108	110
C(15)-O(16)-C (1)-C (2)	-174	-169
O(16)-C (1)-C (2)-C (3)	134	117
C (4)-C (5)-O (5)-C (1')	-103	-110
C (5)-O (5)-C (1')-C(2')	169	172
C(3')-C(4')-O(4')-C(1")	147	134
C(4')-O(4')-C(1")-C(2")	180	163

a) Angle A-B-C-D is considered positive if the A-B bond has to be rotated clockwise to eclipse the C-D bond when looking from B to C.

eters. The positions of solvent molecule, 1,2-dichloroethane in **1** and MeOH in **3** were determined from the difference Fourier map, respectively, but the positions of all hydrogen atoms were not definitely determined. Final R values were 0.096 in **1** and 0.082 in **3**.

All crystallographic calculations were performed on a Silicon Graphics Indigo Elan R4000 workstation using the Crystan-GM programs.[7]

Acknowledgments

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Table 2. Summary of cell paramerters, data collection and refinement details for leucomycin A_5 (**1**) and rokitamycin monomethylacetal (**3**).

Compound	1	3
Chemical formula	$C_{39}H_{65}NO_{14} \cdot 2(CH_2Cl)_2$	$C_{43}H_{73}NO_{16} \cdot CH_3OH$
Formula weight	969.87	892.09
Crystal size (mm^3)	0.30*0.20*0.15	0.20*0.15*0.15
Crystal system	Monoclinic	Monoclinic
a(Å)	21.272(7)	13.052(4)
b(Å)	9.490(3)	20.957(5)
c(Å)	13.033(3)	9.234(2)
β(°)	95.70(2)	92.97(2)
V($Å^3$)	2620(1)	2522(1)
Space group	P 2_1	P 2_1
Z	2	2
Dcalc (g cm^{-3})	1.23	1.18
Unique reflections	3317	3837
Reflections with I > 3 σ (I)	2255	2516
Weighting scheme	$w = \exp(15\sin^2\theta/\lambda^2)/(\sigma^2(Fo)+0.0001Fo^2)$	$w = \exp(10\sin^2\theta/\lambda^2)/(\sigma^2(Fo)+0.0001Fo^2)$
R	0.096	0.082
Rw	0.110	0.091

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