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Crystal and Molecular Structure of 3,6-Dioxograyanotoxin I

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Synopsis. The structure of 3,6-dioxograyanotoxin I ((14*R*)-14-acetoxy-5,10,16-trihydroxygrayanotoxane-3,6-dione) is based on four rings with various conformations. The mutual ring junction of the molecule is the same as that of grayanotoxin I.

Grayanotoxin I is a grayanane diterpenoid and one of the toxic substances in the plants such as *Leucothoe grayana* Max., *Pieris japonica* D. Don, and *Rhododendron japonicum* Suringer. A number of grayanotoxins have been subjected to X-ray diffraction analyses in crystalline state.[1,2] They are composed of four rings and their chemical activities are highly dependent on the ring conformation. In this paper, we report on the X-ray crystal structure determination of 3,6-dioxograyanotoxin I and discuss the molecular architecture.

Experimental

Grayanotoxin I was isolated from the young leaves of *Leucothoe grayana* Max. and was purified by chromatography on silica gel. The grayanotoxin I thus purified was then subjected to Sarett oxidation in absolute pyridine at room temperature to convert to its 3,6-dioxo derivative.

Colorless, prismatic crystals of the 3,6-dioxograyanotoxin I were grown by slow evaporation from ethyl acetate solution at room temperature. A crystal with approximate dimensions of 0.3×0.3×0.4 mm was used for data collection on a Rigaku automated four-circle diffractometer equipped with a rotating-anode X-ray generator operated at 40 kV, 200 mA. Unit-cell parameters were accurately determined by the least squares method from 20 reflections in the range $58° \leqq 2\theta \leqq 61°$. The crystal data are shown in Table 1.

Integrated intensities were measured by the θ-2θ scan technique using Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å) and a monitor count technique. The scan width was $\Delta\theta = (1.2 + 0.15 \tan\theta)°$ and scan speed 2° min^{-1}. Background intensities were measured for 7 s at both ends of a scan. Two sets of reflections; $h\ k\ l$ range, $-11 \leqq h \leqq 11$, $-12 \leqq k \leqq 12$, $0 \leqq l \leqq 10$, a total of 3437 reflections were collected up to $2\theta = 120°$, and 12 reflections were considered as unobserved. Three standard reflections (2 2 6, $\bar{5}$ 1 5, and 6 $\bar{3}$ $\bar{2}$) were measured after every 100 reflections to monitor crystal stability and orientation. No intensity decrease was observed during data collection. Corrections were made for usual Lorentz and polarization effect but not for absorption nor extinction. The two sets of reflection data were averaged for symmetry-related reflections to give 1700 independent reflections ($R_{\mathrm{int}} = 0.009$) after confirmation of no significant Bijvoet difference.

Table 1. Crystal Data

Mol. formula	$C_{22}H_{32}O_7$
Mol. weight	408.48
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions	a/Å=10.293(2)
	b/Å=11.522(4)
	c/Å=9.525(1)
	β/°=106.22(1)
V/Å^3	1084.6(4)
Z	2
D_c/g cm^{-3}	1.251
μ(Cu $K\alpha$)/cm^{-1}	7.70
F(000)	440

Structure Analysis and Refinement

The structure was solved by direct methods with the SHELX86 program.[3] The locations of all the non-hydrogen atoms were performed by alternatively apply-

Table 2. Final Atomic Coordinates and Their Equivalent Isotropic Thermal Parameters[a)]

Atom	x	y	z	B_{eq}/Å^2
O(1)	−0.1650(4)	0.4064(0)	0.9488(5)	4.7(2)
O(2)	0.2193(4)	0.4725(6)	0.9791(5)	2.8(1)
O(3)	0.3876(4)	0.2976(6)	1.1169(4)	4.0(2)
O(4)	0.1152(5)	0.3176(6)	0.5441(5)	4.0(2)
O(5)	0.3368(4)	0.0025(6)	0.7205(4)	3.3(1)
O(6)	0.1323(5)	−0.0467(7)	0.5886(6)	7.5(2)
O(7)	0.6099(4)	0.0199(6)	0.7366(5)	3.2(1)
C(1)	0.1042(5)	0.3419(6)	0.7896(5)	2.5(2)
C(2)	−0.0312(6)	0.4047(7)	0.7766(6)	3.1(2)
C(3)	−0.0603(6)	0.3831(7)	0.9219(6)	3.2(2)
C(4)	0.0636(5)	0.3286(7)	1.0310(6)	3.0(2)
C(5)	0.1775(5)	0.3550(6)	0.9537(6)	2.5(2)
C(6)	0.2997(5)	0.2746(7)	1.0062(6)	2.7(2)
C(7)	0.3082(6)	0.1711(7)	0.9133(6)	2.8(2)
C(8)	0.3660(5)	0.2072(7)	0.7853(5)	2.4(2)
C(9)	0.3317(5)	0.3327(7)	0.7259(6)	2.6(2)
C(10)	0.1806(5)	0.3750(7)	0.6791(6)	2.7(2)
C(11)	0.4029(6)	0.3563(7)	0.6049(6)	3.5(2)
C(12)	0.3994(7)	0.2548(8)	0.5001(7)	3.9(2)
C(13)	0.4299(5)	0.1376(7)	0.5774(6)	3.0(2)
C(14)	0.3227(5)	0.1195(7)	0.6576(6)	2.8(2)
C(15)	0.5254(5)	0.1946(7)	0.8320(6)	2.7(2)
C(16)	0.5642(5)	0.1378(7)	0.7025(6)	2.9(2)
C(17)	0.6839(7)	0.1940(9)	0.6635(9)	4.0(3)
C(18)	0.0335(7)	0.1975(8)	1.0365(10)	4.4(3)
C(19)	0.0891(7)	0.3843(9)	1.1807(7)	4.4(2)
C(20)	0.1793(7)	0.5072(8)	0.6534(8)	3.9(2)
C(21)	0.2363(6)	−0.0726(7)	0.6753(6)	3.4(2)
C(22)	0.2682(8)	−0.1871(8)	0.7466(11)	4.8(3)

a) Equivalent isotropic B_{eq} defined as $B_{\mathrm{eq}} = (4/3)\sum\sum B_{ij}\boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

ing Fourier syntheses and diagonal approximation least-squares.[4)] The structure was further refined by the full-matrix least-squares procedure using the FMLS program:[5)] The function minimized being $\sum w(F_o-F_c)^2$ with $w=1.0$. Non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were found from difference Fourier maps and refined isotropically in the subsequent refinements. The final stage of the refinement having 390 variables yields R (R_w)=0.039 (0.047), goodness-of-fit S=0.458, and ratio of maximum least-squares shift to error $(\Delta/\sigma)_{max}=0.007$ for 1685 non-zero independent reflections with $F_o \geqq 3\sigma(F_o)$. Maximum positive and negative electron densities in the final difference Fourier maps were +0.20 e$Å^{-3}$ and −0.13 e$Å^{-3}$, respectively. The atomic scattering factors used for non-hydrogen atoms were taken from International Tables[6)] and for hydrogen atoms from Stewart et al.[7)] The final atomic parameters are listed in Table 2.[#]

All computations were carried out on an NEC PC-9801 personal computer and an ACOS-S830 computer at the Institute for Protein Research, Osaka University.

Results and Discussion

Figure 1 shows in (a) an ORTEP-II[8)] drawing of the molecule with the atom-numbering scheme and in (b) a chemical structural diagram of the molecule. Bond lengths and bond angles are given in Table 3.

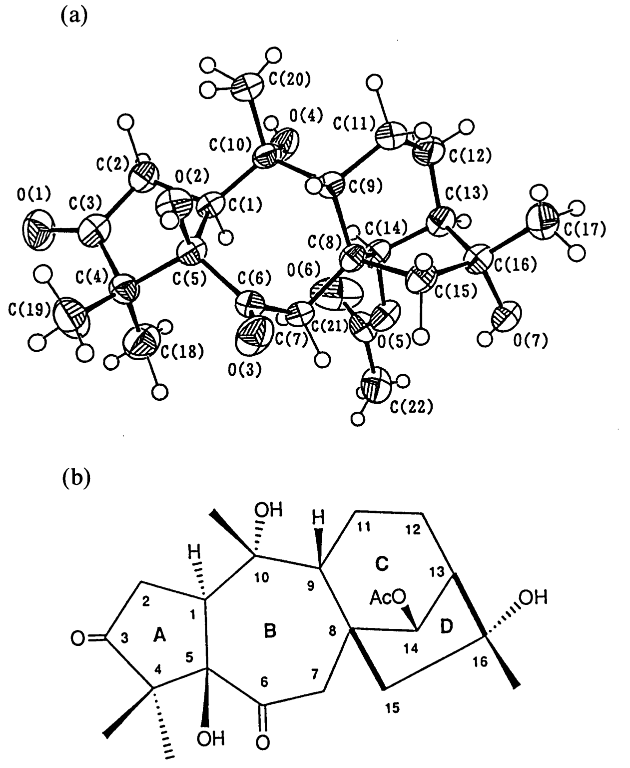

Fig. 1. (a) ORTEP drawing of the molecule with the atom-numbering scheme. The thermal ellipsoids correspond to 50% probability level. (b) A chemical structural diagram of the molecule.

Table 3. Bond Lengths (l/Å) and Bond Angles (ϕ/°)

Bond lengths (l/Å)

O(1)–C(3)	1.206(8)	C(5)–C(6)	1.53(1)
O(2)–C(5)	1.420(9)	C(6)–C(7)	1.50(1)
O(3)–C(6)	1.21(1)	C(7)–C(8)	1.56(1)
O(4)–C(10)	1.44(1)	C(8)–C(9)	1.56(1)
O(5)–C(14)	1.47(1)	C(8)–C(14)	1.55(1)
O(5)–C(21)	1.33(1)	C(8)–C(15)	1.58(1)
O(6)–C(21)	1.19(2)	C(9)–C(10)	1.57(1)
O(7)–C(16)	1.44(1)	C(9)–C(11)	1.55(1)
C(1)–C(2)	1.55(1)	C(10)–C(20)	1.54(2)
C(1)–C(5)	1.54(1)	C(11)–C(12)	1.53(2)
C(1)–C(10)	1.53(1)	C(12)–C(13)	1.53(2)
C(2)–C(3)	1.52(2)	C(13)–C(14)	1.52(1)
C(3)–C(4)	1.54(1)	C(13)–C(16)	1.55(2)
C(4)–C(5)	1.58(1)	C(15)–C(16)	1.54(1)
C(4)–C(18)	1.55(2)	C(16)–C(17)	1.53(2)
C(4)–C(19)	1.52(2)	C(21)–C(22)	1.48(2)

Bond angles (ϕ/°)

C(14)–O(5)–C(21)	119.2(7)	C(14)–C(8)–C(15)	102.1(6)
C(2)–C(1)–C(5)	102.1(6)	C(8)–C(9)–C(10)	119.8(6)
C(2)–C(1)–C(10)	117.0(6)	C(8)–C(9)–C(11)	109.0(6)
C(5)–C(1)–C(10)	118.3(6)	C(10)–C(9)–C(11)	111.8(6)
C(1)–C(2)–C(3)	104.7(6)	O(4)–C(10)–C(1)	107.4(6)
O(1)–C(3)–C(2)	125.0(7)	O(4)–C(10)–C(9)	106.9(6)
O(1)–C(3)–C(4)	124.8(7)	O(4)–C(10)–C(20)	109.4(6)
C(2)–C(3)–C(4)	110.2(7)	C(1)–C(10)–C(9)	112.7(6)
C(3)–C(4)–C(5)	101.0(6)	C(1)–C(10)–C(20)	111.9(6)
C(3)–C(4)–C(18)	106.6(7)	C(9)–C(10)–C(20)	108.4(6)
C(3)–C(4)–C(19)	110.8(7)	C(9)–C(11)–C(12)	114.8(7)
C(5)–C(4)–C(18)	112.8(7)	C(11)–C(12)–C(13)	113.4(7)
C(5)–C(4)–C(19)	113.6(7)	C(12)–C(13)–C(14)	106.4(7)
C(18)–C(4)–C(19)	111.4(7)	C(12)–C(13)–C(16)	112.8(7)
O(2)–C(5)–C(1)	107.8(6)	C(14)–C(13)–C(16)	103.3(6)
O(2)–C(5)–C(4)	109.5(6)	O(5)–C(14)–C(8)	107.7(6)
O(2)–C(5)–C(6)	109.9(6)	O(5)–C(14)–C(13)	109.2(6)
C(1)–C(5)–C(4)	103.7(6)	C(8)–C(14)–C(13)	102.4(6)
C(1)–C(5)–C(6)	113.4(6)	C(8)–C(15)–C(16)	107.1(6)
C(4)–C(5)–C(6)	112.4(6)	O(7)–C(16)–C(13)	109.6(6)
O(3)–C(6)–C(5)	119.9(7)	O(7)–C(16)–C(15)	111.1(6)
O(3)–C(6)–C(7)	122.3(7)	O(7)–C(16)–C(17)	102.7(7)
C(5)–C(6)–C(7)	117.8(6)	C(13)–C(16)–C(15)	103.9(6)
C(6)–C(7)–C(8)	110.3(6)	C(13)–C(16)–C(17)	114.8(7)
C(7)–C(8)–C(9)	115.8(6)	C(15)–C(16)–C(17)	114.9(7)
C(7)–C(8)–C(14)	110.7(6)	O(5)–C(21)–O(6)	122.0(8)
C(7)–C(8)–C(15)	110.4(6)	O(5)–C(21)–C(22)	112.4(7)
C(9)–C(8)–C(14)	109.5(6)	O(6)–C(21)–C(22)	125.6(8)
C(9)–C(8)–C(15)	107.4(6)		

The molecule is based on four rings with various conformations. Ring A takes an envelope conformation, with C(5) atom deviating significantly from the mean plane formed by the remaining four atoms, and ring D a deformed envelope conformation. Ring B adopts a boat conformation with an approximate mirror plane bisecting the C(5)–C(6) bond through the C(9) atom, while ring C has a conformation with a typical chair form. The mutual ring junction of the molecule is the same as that of grayanotoxin I. As shown in Fig. 1-(b), the tetracyclic structure has a *trans*-junction between the rings A and B and a *cis*-junction between the rings B and C. O(1)–C(3) bond distance in the ring A and O(3)–C(6) bond distance in the ring B, 1.206(8) Å and 1.212(10) Å, respectively, show a typical C=O bond

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[#] List of observed and calculated structure factors, anisotropic thermal parameters, and H-atom parameters have been deposited as Document No. 9035 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Table 4. Summary of Hydrogen Bonds, X–H···Y

X	Y	X···Y (l/Å)	H···Y (l/Å)	X–H···Y (ϕ/°)
Intramolecular				
O(2)	O(3)	2.741(9)	2.52(8)	103(8)
O(7)	O(5)	2.780(9)	2.32(8)	124(8)
Intermolecular				
O(2)	O(7)$^{a)}$	2.840(9)	2.20(8)	176(9)
O(7)$^{a)}$	O(3)	2.914(9)	2.39(8)	132(8)
O(4)	O(6)$^{b)}$	2.955(10)	2.35(9)	157(10)

a) and b) are atoms with equivalent positions of $1-x$, $\frac{1}{2}+y$, $2-z$ and $-x$, $\frac{1}{2}+y$, $1-z$, respectively.

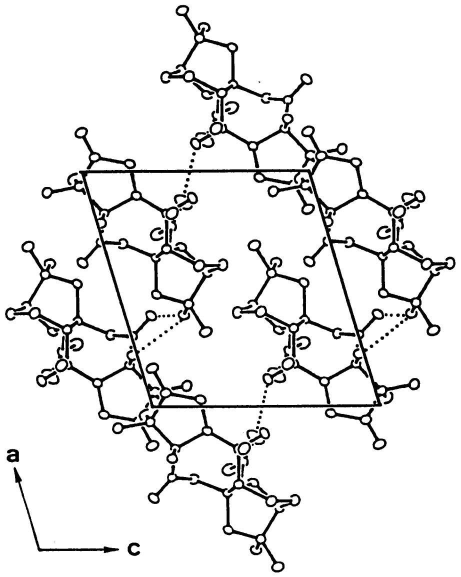

Fig. 2. Crystal structure of the molecules viewed along the *b* axis. Dotted lines show intermolecular hydrogen bonds.

distance, thus significantly different from the distances corresponding to those of grayanotoxin I, in which hydroxyl groups bind to the C(3) and C(6) atom.

All the oxygen atoms, except O(1) atom, participate in hydrogen bonding (Table 4). H(1) atom, which binds to O(2) atom, forms an intermolecular hydrogen bond to O(7) atom but fairly unfavorable to the intramolecular hydrogen bond to O(3) atom. In contrast, H(3) atom that binds to O(7) atom interacts equally with both of O(3) and O(5) atoms, with intermolecular and intramolecular hydrogen bonds, respectively. The crystal structure of the molecules viewed along the *b* axis is shown in Fig. 2. All the intermolecular contacts other than the hydrogen bonds are usual van der Waals distances.

References

1) A. Furusaki, N. Hamanaka, and T. Matsumoto, *Bull. Chem. Soc. Jpn.*, **53**, 1956 (1980); A. Furusaki, S. Gasa, R. Ikeda, and T. Matsumoto, *ibid.*, **54**, 49 (1981); A. Furusaki, S. Gasa, R. Ikeda, T. Matsumoto, N. Yasuoka, and Y. Matsuura, *ibid.*, **54**, 657 (1981); see also references cited therein.

2) P. Narayanan, M. Rohrl, K. Zechmeister, and W. Hoppe, *Tetrahedron Lett.*, **1970**, 3943.

3) G. M. Sheldrick, "Program for the Solution of Crystal Structures," University of Göttingen, Germany (1986).

4) N. Tanaka, K. Yamanouchi, Y. Katsube, and T. Ashida, *J. Crystallogr. Soc. Jpn.*, **31**, 27 (1989).

5) T. Ashida, "The Universal Crystallographic Computing System-Osaka," The Computing Center, Osaka University, Japan (1979), p. 60.

6) "International Tables for X-Ray Crystallography," The Kynoch Press, Birmingham (1974), Vol. IV.

7) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

8) C. K. Johnson, "ORTEP-II, Report ORLN-5138," Oak Ridge National Laboratory, Tennessee, U.S.A. (1976).