ANALYTICAL SCIENCES 2003, VOL. 19

Crystal Structure of Streptozocin

Masayuki HARAMURA,* Akito TANAKA,* Toshio AKIMOTO, and Noriaki HIRAYAMA**†**

**Reverse Proteomics Research Institute Co. Ltd., 2-6-7 Kazusa-Kamatari, Kisarazu, Chiba 292-0818, Japan*
***Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Boseidai, Isehara, Kanagawa 259-1193, Japan*

The crystal belongs to space group $P2_12_12_1$, and the cell dimensions are a = 8.5300(5), b = 11.4516(9) and c = 23.893(1)Å. The final R value is 0.047. There are two crystallographically independent molecules in an asymmetric unit. The pyranose rings in both molecules take chair conformations. The nitrosourea moieties are planar. There is an extensive hydrogen network in the crystal.

(Received August 8, 2003; Accepted October 27, 2003; Published on Web December 17, 2003)

Streptozocin (2-deoxy-2-[[(methylnitrosoamino)carbonyl]amino]-D-glucopyranose)(Fig. 1) is an antibiotic derived from *Streptomyces acromogenes*. This naturally occurring nitrosourea is useful in the treatment of human pancreatic islet cell carcinoma and malignant carcinoid tumors. It also has a high affinity for β cells of the islets of Langerhans and causes diabetes in experimental animals.[3] Although nitrosoureas appear to function as bifunctional alkylating agents, the molecular mechanism of the function of the title compound has not been disclosed so far. To understand the molecular mechanism of the drug action, an X-ray analysis of the title compound was undertaken.

Suitable single crystals for X-ray diffraction experiments were obtained from an acetone solution. A colorless chip crystal having approximate dimensions of 0.25 × 0.15 × 0.10 mm was mounted on a glass fiber. The crystal and experimental data are given in Table 1.

The structure was solved by direct methods and refined by full-matrix least-squares methods with anisotropic temperature factors for non-H atoms. The absolute configuration of the molecule was suggested by referring to that of D-glucose. All H atoms which are bonded to carbon atoms were calculated geometrically and refined using the riding model. Other H atoms bonded to oxygen and nitrogen atoms were located from difference Fourier syntheses. These H atoms were refined with isotropic temperature factors. The atomic parameters for non-H atoms are listed in Table 2.

There are two crystallographically independent molecules of streptozocin in an asymmetric unit. ORTEP III[4] drawings of the molecules together with the atomic numbering are shown in Fig. 2. The two independent molecules adopt essentially similar structures. Selected bond distances and angles are given in Table 3. The bond distances and angles are within the expected ranges. The bond angles around the O106–C107 and N102–N103 bonds and those around the O206–C207 and N202–N203 bonds are highly asymmetrical. The pyranose rings in both molecules take chair conformations. Although the hydroxyl groups at C102 and C202 are axial, all other functional groups attached to the pyranose ring are equatorial. Both of the nitrosourea groups are almost planar, but the orientations of these groups relative to the pyranose rings are different. In molecule I, the torsion angles, C107–N101–C102–C103 and C107–N101–C102–C101, are –169.7(6) and 68.4(8)°, respectively. The corresponding angles in molecule II, however, are –146.3(6) and 90.0(7)°, respectively. In the crystal there is an extensive hydrogen-bonding network. The geometrical details of the hydrogen bonds are tabulated in Table 4. There are ten intermolecular hydrogen bonds and ten intramolecular hydrogen bonds. All potential hydrogen-bond donors and acceptors, except for N203, are engaged in the hydrogen bonds.

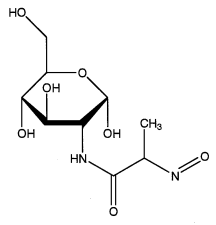

Fig. 1 Chemical structure of streptozocin.

Table 1 Crystal and experimental data

Formula: $C_8H_{15}N_3O_7$	
Formula weight = 265.22	
Crystal system: orthorhombic	
Space group: $P2_12_12_1$	Z = 8
a = 8.5300(5)Å	
b = 11.4516(9)Å	
c = 23.893(1)Å	
V = 2333.9(3)Å^3	
D_x = 1.51 g/cm^3	
No. observations ($I > 2.00\sigma(I)$) = 2360	
No. parameters = 402	
θ_{max} = 68.18° with Cu K_α	
R ($I > 2.00\sigma(I)$) = 0.047	
$Rw(F_o^2)$ = 0.1170	
Weighting scheme: $w = 1/[0.0013F_o^2 + 1.000\sigma(F_o^2)]/(4F_o^2)$	
$(\Delta/\sigma)_{max}$ = 0.004	
$(\Delta\rho)_{max}$ = 0.50e/Å^3	
$(\Delta\rho)_{min}$ = –0.44 e/Å^3	
Measurement : Rigaku RAXIS-RAPID	
Program system : CrystalStructure Ver. 3.5.1[1]	
Structure determination : SIR92[2]	
Refinement : full-matrix	

† To whom correspondence should be addressed.
E-mail address: hirayama@is.icc.u-tokai.ac.jp

Table 2 Atomic coordinates and equivalent isotropic thermal parameters (B_{eq})

Atom	*x*	*y*	*z*	B_{eq}
		molecule I of streptozocin		
O101	0.6670(6)	-0.2927(4)	1.0764(2)	3.2(1)
O102	0.3909(6)	-0.2309(4)	1.2169(2)	2.9(1)
O103	0.5814(7)	-0.4331(4)	1.2444(2)	3.0(1)
O104	0.5201(5)	-0.4616(4)	1.0934(2)	2.8(1)
O105	0.4737(7)	-0.6629(4)	1.1782(2)	4.1(1)
O106	0.2753(6)	-0.1728(4)	1.0274(2)	3.1(1)
O107	0.3442(8)	0.1795(4)	1.0980(3)	6.9(2)
N101	0.4102(7)	-0.1500(5)	1.1074(2)	2.4(1)
N102	0.3136(6)	0.0126(5)	1.0598(2)	2.9(1)
N103	0.3673(8)	0.0729(5)	1.1025(3)	4.8(2)
C101	0.517(1)	-0.3415(6)	1.0785(3)	2.7(2)
C102	0.4204(9)	-0.2735(6)	1.1207(2)	2.3(2)
C103	0.4909(9)	-0.2895(6)	1.1784(3)	2.3(2)
C104	0.5070(9)	-0.4182(5)	1.1916(3)	2.3(2)
C105	0.596(1)	-0.4819(6)	1.1453(3)	2.8(2)
C106	0.611(1)	-0.6112(6)	1.1551(3)	3.5(2)
C107	0.3328(8)	-0.1119(6)	1.0638(3)	2.4(1)
C108	0.232(1)	0.0662(7)	1.0134(3)	5.3(2)
		molecule II of streptozocin		
O201	0.6205(6)	-0.0308(4)	1.1829(2)	2.9(1)
O202	1.0330(7)	-0.1500(6)	1.1057(3)	5.5(2)
O203	1.0694(7)	-0.1840(5)	1.2257(3)	4.5(2)
O204	0.8305(5)	0.0786(3)	1.2168(2)	2.8(1)
O205	1.1088(6)	0.1146(5)	1.2744(2)	4.2(1)
O206	0.7940(8)	0.1538(5)	1.0378(2)	6.5(2)
O207	0.5451(6)	-0.1092(5)	0.9365(2)	4.6(1)
N201	0.7543(7)	-0.0273(5)	1.0734(2)	3.0(1)
N202	0.6619(7)	0.0222(5)	0.9839(2)	3.7(1)
N203	0.6091(8)	-0.0868(5)	0.9806(2)	3.5(1)
C201	0.7383(8)	0.0495(5)	1.1698(3)	2.6(2)
C202	0.8407(8)	-0.0020(5)	1.1247(3)	2.6(1)
C203	0.9220(8)	-0.1105(6)	1.1465(3)	3.0(2)
C204	1.0111(8)	-0.0808(6)	1.1992(3)	3.3(2)
C205	0.9074(8)	-0.0182(6)	1.2410(3)	2.9(2)
C206	0.9970(9)	0.0281(6)	1.2903(3)	3.9(2)
C207	0.743(1)	0.0550(7)	1.0340(3)	3.9(2)
C208	0.646(1)	0.1032(7)	0.9379(3)	6.9(3)

$B_{eq} = 8/3\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U^{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

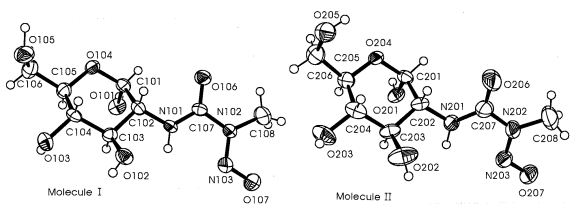

Fig. 2 Molecular structures of streptozocin with atom labeling. Thermal ellipsoids of non-H atoms are drawn at the 50% probability level.

Table 3 Selected bond lengths(Å) and angles (˚)

molecule I of streptozocin			molecule II of streptozocin		
O(101) -	C(101)	1.397(10)	O(201) -	C(201)	1.398(8)
O(102) -	C(103)	1.423(9)	O(202) -	C(203)	1.432(10)
O(103) -	C(104)	1.422(9)	O(203) -	C(204)	1.430(9)
O(104) -	C(101)	1.421(8)	O(204) -	C(201)	1.411(8)
O(104) -	C(105)	1.418(9)	O(204) -	C(205)	1.412(8)
O(105) -	C(106)	1.424(10)	O(205) -	C(206)	1.427(9)
O(106) -	C(107)	1.218(8)	O(206) -	C(207)	1.216(10)
O(107) -	N(103)	1.241(7)	O(207) -	N(203)	1.214(7)
N(101) -	C(102)	1.452(9)	N(201) -	C(202)	1.459(9)
N(101) -	C(107)	1.308(9)	N(201) -	C(207)	1.336(9)
N(102) -	N(103)	1.314(8)	N(202) -	N(203)	1.329(8)
N(102) -	C(107)	1.438(9)	N(202) -	C(207)	1.433(9)
N(102) -	C(108)	1.446(9)	N(202) -	C(208)	1.445(9)

molecule I of streptozocin				molecule II of streptozocin			
C(101) -	O(104) -	C(105)	112.7(5)	C(201) -	O(204) -	C(205)	113.5(4)
C(102) -	N(101) -	C(107)	122.0(6)	C(202) -	N(201) -	C(207)	119.2(6)
N(103) -	N(102) -	C(107)	115.4(5)	N(203) -	N(202) -	C(207)	117.3(5)
N(103) -	N(102) -	C(108)	122.7(6)	N(203) -	N(202) -	C(208)	121.7(5)
C(107) -	N(102) -	C(108)	121.8(6)	C(207) -	N(202) -	C(208)	120.8(6)
O(107) -	N(103) -	N(102)	113.2(7)	O(207) -	N(203) -	N(202)	113.7(5)
O(101) -	C(101) -	O(104)	112.3(6)	O(201) -	C(201) -	O(204)	112.2(5)
O(101) -	C(101) -	C(102)	108.4(6)	O(201) -	C(201) -	C(202)	108.6(5)
O(104) -	C(101) -	C(102)	109.9(6)	O(204) -	C(201) -	C(202)	109.8(5)
N(101) -	C(102) -	C(101)	112.8(5)	N(201) -	C(202) -	C(201)	112.7(6)
N(101) -	C(102) -	C(103)	109.9(5)	N(201) -	C(202) -	C(203)	110.9(5)
O(102) -	C(103) -	C(102)	107.1(6)	O(202) -	C(203) -	C(202)	109.1(6)
O(102) -	C(103) -	C(104)	112.3(6)	O(202) -	C(203) -	C(204)	107.8(6)
O(103) -	C(104) -	C(103)	110.0(5)	O(203) -	C(204) -	C(203)	111.0(6)
O(103) -	C(104) -	C(105)	111.3(6)	O(203) -	C(204) -	C(205)	107.6(6)
O(104) -	C(105) -	C(104)	109.2(6)	O(204) -	C(205) -	C(204)	111.9(6)
O(104) -	C(105) -	C(106)	109.6(6)	O(204) -	C(205) -	C(206)	106.3(5)
O(105) -	C(106) -	C(105)	113.6(6)	O(205) -	C(206) -	C(205)	112.1(6)
O(106) -	C(107) -	N(101)	125.5(6)	O(206) -	C(207) -	N(201)	125.3(7)
O(106) -	C(107) -	N(102)	118.3(6)	O(206) -	C(207) -	N(202)	118.6(7)
N(101) -	C(107) -	N(102)	116.2(6)	N(201) -	C(207) -	N(202)	116.0(7)

Table 4 Hydrogen bonds. A and D denote the hydrogen-bond acceptor and donor, respectively.

D-H···A	D-H(Å)	H···A(Å)	D···A(Å)	∠D-H···A(°)
O(105)- H(4) ··· O(107)^{i}	0.96(9)	1.91(9)	2.855(8)	170(8)
O(203)- H(14) ··· O(102)^{ii}	0.81(9)	2.00(9)	2.802(8)	168(9)
O(101)- H(15) ··· O(106)^{iii}	0.85(7)	1.84(7)	2.676(7)	170(7)
O(202)- H(16) ··· O(207)^{iii}	0.75(9)	2.26(9)	2.938(9)	151(9)
O(102)- H(22) ··· O(105)^{iv}	0.71(7)	2.18(7)	2.867(7)	163(7)
O(201)- H(25) ··· O(103)^{iv}	0.89(6)	1.81(5)	2.690(7)	168(5)
O(205)- H(26) ··· O(203)^{v}	0.84(7)	2.04(7)	2.762(8)	144(7)
O(103)- H(29) ··· O(205)^{vi}	0.69(9)	2.05(8)	2.736(8)	173(8)
C(208)- H(19) ···O(107)^{vii}	0.952(11)	2.377(10)	3.128(10)	135.6(7)
C(108)- H(27) ···O(104)^{viii}	0.950(11)	2.534(9)	3.349(9)	143.9(8)
N(201)- H(9) ··· O(101)	1.04(7)	2.14(7)	3.130(7)	159(6)
N(101)- H(12) ··· O(201)	0.85(5)	2.06(6)	2.887(7)	165(6)
C(103)- H(11) ··· O(201)	0.91(6)	2.60(5)	3.164(8)	121(4)
N(101)- H(12) ···N(103)	0.85(5)	2.30(6)	2.581(8)	100(4)
O(205)- H(26) ···O(204)	0.84(7)	2.44(7)	2.775(7)	105(5)
C(105)- H(7) ···O(101)	0.91(7)	2.38(5)	2.788(8)	107(4)
C(103)- H(11) ···O(101)	0.91(6)	2.53(5)	2.863(9)	102(3)
C(101)- H(17) ···O(106)	0.84(7)	2.57(6)	3.078(9)	120(5)
C(208)- H(19) ···O(206)	0.95(1)	2.325(9)	2.762(9)	107.3(7)
C(108)- H(27) ···O(106)	0.95(1)	2.360(9)	2.782(9)	106.4(7)

symmetry code: (i) x, –1 + y, z (ii) 1 + x, y, z (iii) 1/2 + x, – 1/2 – y, 2 – z (iv) 1 – x, 1/2 + y, 5/2 – z (v) 2 – x, 1/2 + y, 5/2 – z (vi) 2 – x, – 1/2 + y, 5/2 – z (vii) 1/2 + x, 1/2 – y, 2 – z (viii) – 1/2 + x, – 1/2 – y, 2 – z

Acknowledgements

This work was supported by Grants for the Key Technology Research Promotion Program of New Energy and Industrial Technology Development Organization (NEDO) of Japan, and also by the Research and Study Program of Tokai University Educational System General Research Organization.

References

1. CrystalStructure, version 3.5.1, **2000** – **2003** Crystal Structure Analysis Package, Rigaku and Rigaku/MSC
2. SIR92 A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, and M. Camalli, *J. Appl. Cryst.*, **1994**, *27*, 435.
3. "*Goodman & Gilman's The Pharmacological Basis of Therapeutics*," ed. J. G. Hardman and L. E. Limbird, 10th ed., **2001**, McGraw-Hill, New York, 1398.
4. ORTEP III L. J. Farrugia, *J. Appl. Cryst.*, **1997**, *22*, 389