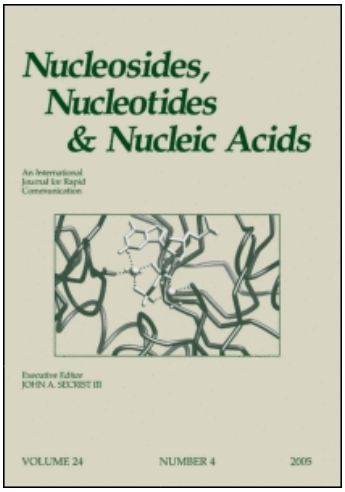

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THE STRUCTURE OF NEPLANOCIN C

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Abstract: The molecular and crystal structure of neplanocin C(3), $C_{11}H_{13}N_5O_4$ M.W. =279.26, has been determined by X-ray anlysis. The space group is $P2_1$ with a=16.381(2), b=8.210(1), c=9.127(1) Å, β=105.31(1)° and z=4. The structure was solved by direct method, and least-squares refinement using 2093 reflections with $|Fo|>3\sigma(F)$ led to the final R value of 0.0772. The sugar puckering of the two crystallographically independent molecules is C(2')-exo-C(3')-endo, and the torsion angles about the N(9)-C(1') bond are 22.8(6) and 28.7(6)°, respectively (anti conformation).

INTRODUCTION

Neplanocins, novel carbocyclic analogues of purine nucleosides, were isolated from the culture filtrate of Ampullariella regularis A11079. They consist of at least five components, named as neplanocin A(1), B(2), C(3), D(4) and F(5), and 1 possesses strong antitumor activity (Fig. 1)[1,2,3]. In an earlier study, the absolute stereochemistry of 1 was elucidated on the basis of a chemical degradation and an X-ray crystal structure analysis[4], but the absolute stereochemistries of the other components have not been determined. Recently, we obtained suitable crystals of 3 for X-ray analysis. In this paper, we report the stereochemistry of 3 by X-ray analysis.

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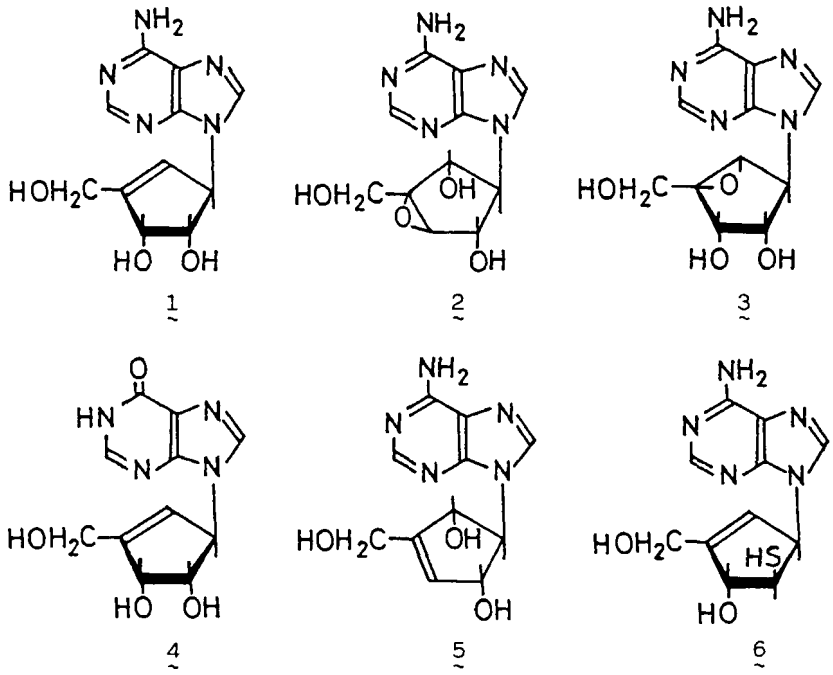


FIG. 1. Chemical structures of neplanocins.

EXPERIMENT AND STRUCTURAL DETERMINATION

Colorless single crystals of 3 were grown from a water solution. The sample used for the X-ray experiment had dimensions of about 0.31 X 0.24 X 0.14 mm^3. The crystal data are given in Table 1. The unit-cell dimensions and diffraction intensities were measured on a Rigaku four-circle diffractometer with graphite-monochromated Mo Kα radiation (λ =0.71069Å). The ω-2θ scan technique was applied at a 2θ scan rate of 4° min^{-1}; the scan width in ω was $(0.9 + 0.34 \tan\theta)^{\circ}$. The background was measured for 15s at each end of the scan range. 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 55°, 2093 independent structure factors above the 3σ(F) level were selected for the structure determination.

The structure was solved by direct methods using the program MULTAN 78[5]. An E-map calculated with a phase set having the highest

TABLE 1. Crystal data of 3

$C_{11}H_{13}N_5O_4$ M.W. =279.26 Monoclinic $P2_1$, z=4,
a=16.381(2), b=8.210(1), c=9.127(1)Å, β=105.31(1)°
U=1183.8(3)Å^3, Dcalc.=1.567g/cm^3

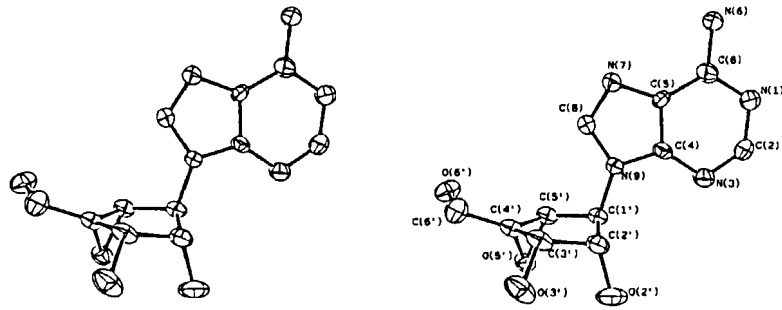
TABLE 2 The atomic coordinates with their estimated standard deviations.

Atom	x/a	y/b	z/c
N(1)A	0.4225(3)	0.1888(5)	0.3489(5)
C(2)A	0.3625(3)	0.1562(6)	0.2187(6)
N(3)A	0.3131(3)	0.2554(5)	0.1207(4)
C(4)A	0.3305(3)	0.4116(6)	0.1603(5)
C(5)A	0.3922(3)	0.4654(6)	0.2865(5)
C(6)A	0.4395(3)	0.3477(7)	0.3848(6)
N(7)A	0.3935(2)	0.6339(5)	0.2941(5)
C(8)A	0.3324(3)	0.6761(6)	0.1717(6)
N(9)A	0.2923(2)	0.5481(5)	0.0879(4)
N(6)A	0.4977(3)	0.3811(5)	0.5130(6)
C(1')A	0.2179(3)	0.5547(6)	-0.0425(5)
C(2')A	0.1344(3)	0.5313(7)	0.0047(5)
O(2')A	0.0776(2)	0.4427(5)	-0.1123(4)
C(3')A	0.1020(3)	0.7069(7)	0.0185(5)
O(3')A	0.0120(2)	0.7153(5)	-0.0284(4)
C(4')A	0.1441(3)	0.8153(6)	-0.0709(5)
C(5')A	0.2128(3)	0.7233(7)	-0.1101(5)
O(5')A	0.1340(2)	0.7491(4)	-0.2242(3)
C(6')A	0.1416(3)	0.9977(7)	-0.0573(6)
O(6')A	0.2051(2)	1.0721(5)	-0.1178(4)
N(1)B	0.5687(3)	0.2129(5)	0.1669(5)
C(2)B	0.6268(3)	0.1806(7)	0.2987(6)
N(3)B	0.6805(2)	0.2819(5)	0.3890(4)
C(4)B	0.6694(3)	0.4349(6)	0.3374(5)
C(5)B	0.6098(3)	0.4883(6)	0.2105(5)
C(6)B	0.5583(3)	0.3692(6)	0.1197(5)
N(7)B	0.6147(2)	0.6550(5)	0.1908(4)
C(8)B	0.6772(3)	0.6994(6)	0.3079(5)
N(9)B	0.7122(2)	0.5721(5)	0.4012(4)
N(6)B	0.5001(3)	0.4023(6)	-0.0109(6)
C(1')B	0.7857(3)	0.5801(6)	0.5372(5)
C(2')B	0.8708(3)	0.5627(7)	0.4969(5)
O(2')B	0.9307(2)	0.4955(5)	0.6227(4)
C(3')B	0.8973(3)	0.7408(7)	0.4713(5)
O(3')B	0.9867(2)	0.7613(6)	0.5104(4)
C(4')B	0.8529(3)	0.8469(7)	0.5633(5)
C(5')B	0.7863(3)	0.7507(6)	0.6014(5)
O(5')B	0.8642(2)	0.7811(4)	0.7149(3)
C(6')B	0.8532(3)	1.0314(7)	0.5495(6)
O(6')B	0.7932(2)	1.1001(5)	0.6193(4)

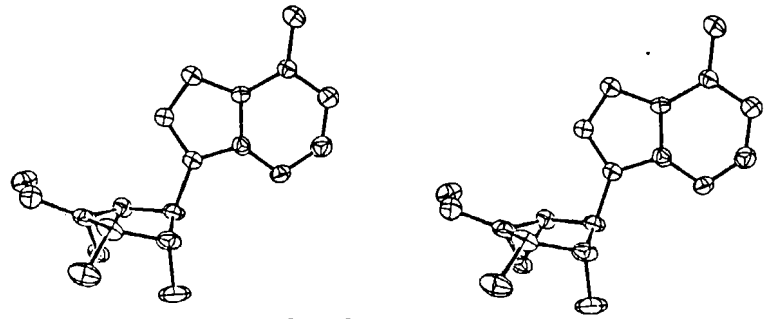
figure-of-merit revealed all the nonhydrogen atoms. Their positional and anisotropic thermal parameters were refined by the block-diagonal least-squares calculations. The final R-factor was 0.0772.

RESULTS AND DISCUSSION

Final atomic coordinates are given in Table 2. The frameworks of the two crystallographically independent molecules, A and B, are illustrated in Fig. 2, while the bond distances and angles are given in Tables 3. The values are consistent with chemical structure shown as 3 in Fig. 1. The crystal structure viewed along the c-axis is shown in Fig. 3. The hydrogen bonds, listed in Table 4, make a three-dimensional network. From Table 3, it is clear that significant differences (more than 3σlevel) are found for parameters involving the atoms N(9), C(1'), C(2')and C(3'). This may be caused by the



Molecule A



Molecule B

FIG. 2. Stereoview of the molecules A and B

TABLE 3. The bond distances and angles with their standard deviations. The e.s.d.'s given in parentheses refer to the last digits.

Bond distance(Å)

Bond	Mol. A	Mol. B	Bond	Mol. A	Mol.B
N(1)-C(2)	1.354(6)	1.348(6)	C(1')-C(2')	1.551(7)	1.540(7)
N(1)-C(6)	1.356(7)	1.350(7)	C(1')-C(5')	1.509(7)	1.518(7)
C(2)-N(3)	1.318(6)	1.328(6)	C(2')-O(2')	1.418(6)	1.410(6)
N(3)-C(4)	1.342(6)	1.337(6)	C(2')-C(3')	1.553(8)	1.560(8)
C(4)-C(5)	1.390(6)	1.374(6)	C(3')-O(3')	1.425(6)	1.423(6)
C(4)-N(9)	1.365(6)	1.373(6)	C(3')-C(4')*	1.494(7)	1.522(8)
C(5)-C(6)	1.405(7)	1.409(6)	C(4')-C(5')	1.476(7)	1.460(7)
C(5)-N(7)	1.385(6)	1.386(6)	C(4')-O(5')	1.468(6)	1.451(6)
C(6)-N(6)	1.328(6)	1.343(6)	C(4')-C(6')	1.504(8)	1.512(8)
N(7)-C(8)	1.333(6)	1.322(5)	C(5')-O(5')	1.445(5)	1.437(5)
N(8)-N(9)*	1.362(6)	1.374(6)	C(6')-O(6')	1.437(7)	1.424(7)
N(9)-C(1')*	1.462(5)	1.486(5)			

Bond angle(°)

Bond	Mol. A	Mol. B	Bond	Mol. A	Mol. B
C(2)-N(1)-C(6)	117.2(4)	118.1(4)	N(9) -C(1')-C(2')	112.1(4)	112.4(4)
N(1)-C(2)-N(3)	130.4(5)	128.8(5)	N(9) -C(1')-C(5')*	108.1(4)	106.5(4)
C(2)-N(3)-C(4)	111.0(4)	111.3(4)	C(2')-C(1')-C(5')	105.7(4)	105.3(4)
N(3)-C(4)-C(5)	125.7(4)	126.7(4)	C(1')-C(2')-O(2')	107.9(4)	108.7(4)
N(3)-C(4)-N(9)	128.1(4)	127.9(4)	C(1')-C(2')-C(3')	104.6(4)	104.7(4)
C(5)-C(4)-N(9)	106.3(4)	105.4(4)	O(2')-C(2')-C(3')*	111.5(4)	109.8(4)
C(4)-C(5)-C(6)	118.0(4)	117.1(4)	C(2')-C(3')-O(3')	111.7(4)	112.4(4)
C(4)-C(5)-N(7)	110.9(4)	111.9(4)	C(2')-C(3')-C(4')*	107.0(4)	105.2(4)
C(6)-C(5)-N(7)	131.1(4)	130.9(4)	O(3')-C(3')-C(4')	113.4(4)	113.9(4)
N(1)-C(6)-C(5)	117.7(4)	117.8(4)	C(3')-C(4')-C(5')	108.6(4)	108.5(4)
N(1)-C(6)-N(6)	117.8(4)	118.4(4)	C(3')-C(4')-O(5')	110.3(4)	110.7(4)
C(5)-C(6)-N(6)	124.5(5)	123.8(5)	C(3')-C(4')-C(6')	121.4(5)	120.8(5)
C(5)-N(7)-C(8)	102.7(4)	103.1(4)	C(5')-C(4')-O(5')	58.8(3)	59.2(3)
N(7)-C(8)-N(9)	114.4(4)	113.5(4)	C(5')-C(4')-C(6')	124.7(5)	125.3(5)
C(4)-N(9)-C(8)	105.7(3)	106.2(3)	O(5')-C(4')-C(6')	116.7(4)	116.6(4)
C(4)-N(9)-C(1')	126.9(4)	127.0(4)	C(1')-C(5')-C(4')	109.5(4)	109.7(4)
C(8)-N(9)-C(1')	127.1(4)	127.7(4)	C(1')-C(5')-O(5')	111.8(4)	110.7(4)
			C(4')-C(5')-O(5')	60.4(3)	60.1(3)
			C(4')-O(5')-C(5')	60.9(3)	60.7(3)
			C(4')-C(6')-O(6')	110.7(5)	110.2(5)

*significant difference between the molecule A and B.

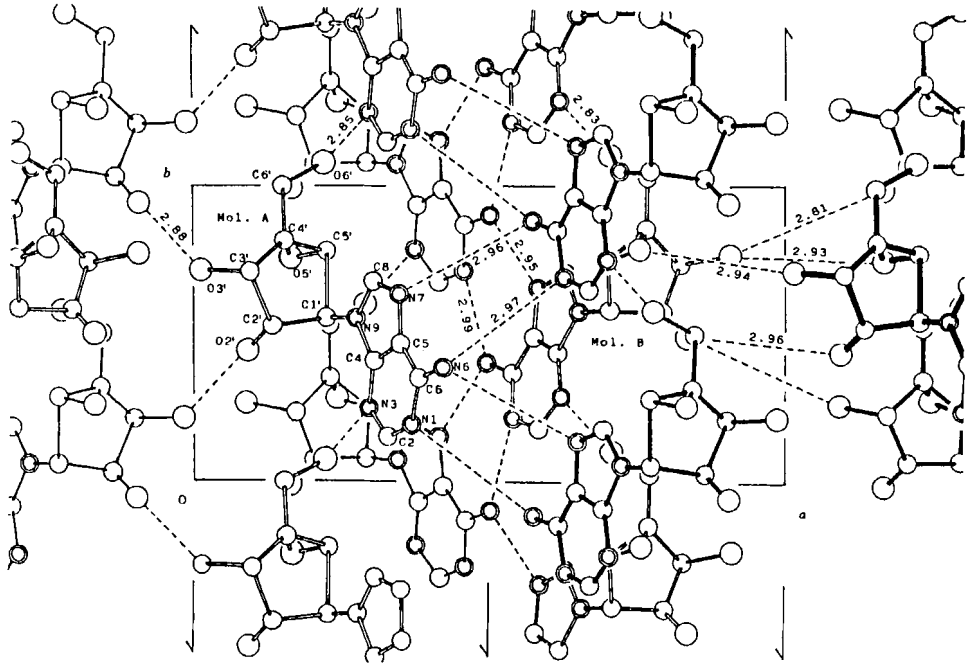


FIG. 3. The molecular arrangement viewed along the c-axis

TABLE 4. Hydrogen bond lengths(Å)

N(6)A---N(1)A$^{V)}$	2.97	N(6)B---N(1)B$^{IV)}$	2.99
N(7)A---N(6)A$^{V)}$	2.96	N(7)B---N(6)B$^{IV)}$	2.95
O(3')A---O(2')A$^{III)}$	2.88	O(3')B---O(2')B$^{VI)}$	2.81
O(5')B---O(3')A$^{II)}$	2.94	O(3')B---O(5')A$^{II)}$	2.93
O(6')A---N(3)A$^{I)}$	2.85	O(6')B---N(3)B$^{I)}$	2.83
O(2')B---O(2')A$^{II)}$	2.96		

Symmetry code

I)	x, 1+y, z	II)	1+x, y, 1+z	III)	-x, 1/2+y, -z
IV)	1-x, 1/2+y, -z	V)	1-x, 1/2+y, 1-z	VI)	2-x, 1/2+y, 1-z

difference in the torsion angles about the N(9)-C(1') bond. However, the overall conformations in both molecules are very similar. The bond lengths and angles of the adenine moiety are in satisfactory agreement with those of 1[4] and 2'(R)-SH-2'-deoxy- neplanocin A(6)[6].

In the cyclopentane ring the bond lengths and angles are in the expected range, and the C(4')---C(5') bond distances are 1.476(7) and 1.460(7)Å for the A and B molecules respectively. Both C(2')-exo-C(3') -endo conformations of the cyclopentane ring found for molecules A and B, respectively, are similar to that of the cyclopentene ring in 1.

The torsion angles about the N(9)-C(1') bond, Φ[C(8)-N(9)- C(1')-C(5')] , are 22.8(6) and 28.7(6)° for molecules A and B, which lie in the range described as anti. The corresponding torsion angle in 1 is 61.3(3)°, and in 6 having 26.3(4)°. The interplanar angle between the adenine plane and the mean cyclopentane plane are 82.2 and 83.5° for molecules A and B respectively.

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