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2′-Deoxycytidine-N(3)-cyanoborane Monohydrate

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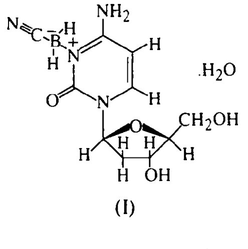
Abstract

The structure of the title compound, [4-amino-1-(2-deoxy-β-D-ribofuranosyl)-2-oxo-1*H*-3-pyrimidinio]-(cyano)borate, $C_{10}H_{15}BN_4O_4.H_2O$, features an interaction of 2.05 (4) Å between an H atom of the —BH_2CN group and an H atom of the —NH_2 group. The —C≡N group does not lie in the cytosine plane, the N atom being 2.24 Å away from the plane. The cytosine rings are stacked with almost complete overlap along the twofold screw axis with an interplanar separation of 4.03 Å. The sugar is in the ^3_4T puckering mode, the C(5′)—O(5′) bond has the *gg* conformation and the relative orientation of the sugar and the base is *anti*.

Comment

Cyanoborane analogs of 2′-deoxynucleosides such as the title compound, (I), show *in vivo* antineoplastic activity against various tumors (Sood, Spielvogel & Shaw, 1989; Sood, Spielvogel, Shaw, Carlton, Burnham, Hall & Hall, 1992). In addition, the title compound has potential use in boron neutron-capture therapy (BNCT) since it tends to concentrate quite effectively in rapidly dividing cancer cells (Sood *et al.*, 1992). The BNCT technique has been used recently in the treatment of brain cancer (see, for example, *Science*, 17 February 1995, Vol. 267, p. 956 and 23 September 1994, Vol. 265, p. 1799).



(I)

In order to provide more insight into the structure–activity relationships of cyanoborane nucleosides we have started a program of research on the structure of these nucleosides using X-ray diffraction and *ab initio* molecular-orbital (MO) calculations. The title nucleoside has been crystallized in a different crystal system by Gao, Sood, Shaw & Williams (1996). Some of the X-ray results described here have been used recently in theoretical computations on intramolecular non-bonded H···H interactions between the —NH_2 and —BH_2CN group H atoms (Zottola, Pedersen, Singh & Shaw, 1994).

The B—H, C—H, N—H and O—H distances have reasonable values and range from 1.04 (3) to 1.08 (3) Å for B, 0.93 (4) to 1.04 (4) Å for C, 0.89 (3) to 0.91 (3) Å for N and 0.71 (5) to 0.83 (4) Å for O. The values of $U_{\rm iso}$ for the H atoms range from 0.03 (1) to 0.08 (1) Å^2. The geometry around the B atom is tetrahedral. The bond angles at B, including those subtended by the H atoms, vary from 107.7 (18)° for C(3)—B—H(1B) to 111.6 (16)° for N(3)—B—H(1B). The B—C—N geometry is approximately linear, the bond angle at C being 178.4 (3)°. Of the two exocyclic bond angles at N(3), C(4)—N(3)—B is larger [123.8 (2)°] than C(2)—N(3)—B [115.0 (2)°]. There is a close van der Waals interaction (Pauling, 1960) of 2.05 (4) Å between one of the >BH_2 group H atoms [H(1B)] and one of the —NH_2 group H atoms [H(1N4)]; this distance is 1.96 Å if the B—H and N—H bond distances are normalized to 1.20 and 1.01 Å, respectively. The intramolecular distance between H(2B) and the carbonyl O atom O(2) is normal [2.62 (3) Å; 2.64 Å if normalized bond lengths are used].

The pyrimidine ring is planar, although the deviations of the atoms from the mean plane are somewhat

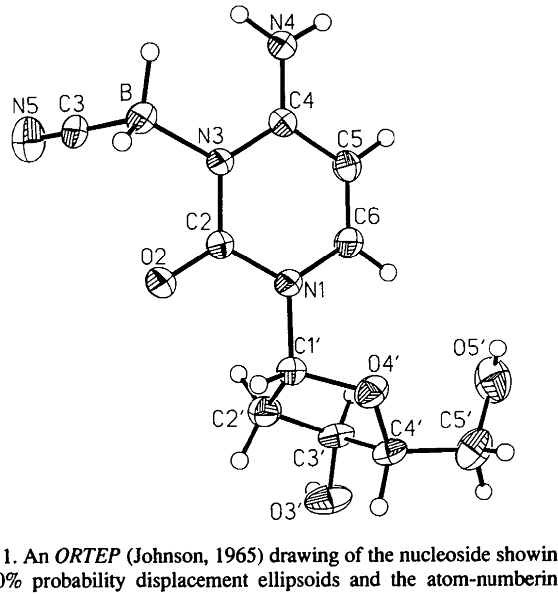


Fig. 1. An *ORTEP* (Johnson, 1965) drawing of the nucleoside showing 50% probability displacement ellipsoids and the atom-numbering scheme. H atoms are shown as small circles of arbitrary size.

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larger than those usually observed [N(1) 0.034 (3), C(2) −0.044 (3), N(3) 0.019 (3), C(4) 0.016 (3), C(5) −0.027 (4), C(6) 0.002 (4) Å]. C(1′), O(2), B and N(4) lie 0.134 (3), −0.155 (3), 0.166 (4) and 0.042 (3) Å, respectively, from the plane of the ring. Comparison of the cytosine ring torsion angles obtained by X-ray diffraction and those calculated by MO optimization with mean values (Taylor & Kennard, 1982), shows the ring to be slightly (but significantly) perturbed from planarity (Table 4).

The six-atom pyrimidine ring plane and the five-atom ribose ring plane are, as usual, almost perpendicular to each other, the dihedral angle between them being 73.5°. The ribose ring has the twist conformation C(3′)*endo*–C(4′)*exo* (${}^3_4T$), the angle of pseudorotation, P, is 32.9° and $\nu_{\max}$, the maximum puckering amplitude, is 36.9° (Altona & Sundaralingam, 1972; Saenger, 1984). The conformation around the exocyclic bond C(4′)—C(5′) is *gauche*$^+$ [C(3′)—C(4′)—C(5′)—O(5′) 53.1 (4), O(4′)—C(4′)—C(5′)—O(5′) −64.8 (4)°]. The glycosyl conformation is *anti*, the torsion angle χ [O(4′)—C(1′)—N(1′)—C(2)] being −150.8 (2)°. An *ORTEP* (Johnson, 1965) view of the molecule with the atom-numbering scheme is shown in Fig. 1.

As the —BH_2CN substitution at N(3) is unusual, we decided to explore the structure further by carrying out a high-level *ab initio* MO calculation using *GAUSSIAN*92 at the STO 6-31G** level of approximation (Frisch *et al.*, 1992). This provided us with the structure *in vacuo* with no influence from intermolecular forces. The MO geometry optimization was carried out starting from the orthogonalized X-ray coordinates. No rotational searches were made. The largest difference in bond lengths given by the two methods is observed for the B—N(3) bond, which is shorter by 0.046 Å from the X-ray diffraction study than from the MO calculation. The B—C(3) bond is also shorter (by 0.023 Å). The following observations may also be noted: (*a*) there are no significant (>0.008 Å) differences in any of the C—C bond distances between the two methods; (*b*) all C—O bond distances are found to be slightly but significantly longer from the X-ray diffraction study than from the MO calculation; and (*c*) the difference in the C(1′)—O(4′) and C(4′)—O(4′) bond distances, attributed to the anomeric effect, is more pronounced from the X-ray study than from the MO calculation [C(1′)—O(4′) 1.407 (3) (X-ray), 1.395 Å (MO); C(4′)—O(4′) 1.446 (3) (X-ray), 1.418 Å (MO)].

The electronic charge density was calculated by Mulliken population analysis and by the algorithm *CHELP* (charges from electrostatic potential), both accessible through the *GAUSSIAN*92 program package (Frisch *et al.*, 1992). The charges on the atoms near the site of substitution, N(3), calculated by the two methods (values calculated using *CHELP* in parentheses) are N(3) −0.866 (−0.579), B 0.290 (0.315), H(1B) −0.146 (−0.233), H(2B) −0.071 (0.162), C(3) 0.073 (0.199), N(5) −0.459 (−0.540), N(4) −0.748 (−1.012), H(1N4) 0.373 (0.468), H(2N4) 0.333 (0.458) and O(2) −0.586 (−0.585 e Å^{-3}). We note that the presence of opposite charges on H(1B) and H(1N4) is consistent with the short intramolecular distance of 2.05 (4) Å between them. Atoms H(2B) and O(2), on the other hand, have a somewhat repulsive interaction as both have negative charges. They are 2.62 (3) Å apart, which is a normal intramolecular non-bonded distance.*

An interesting pattern of electrostatic charge distribution for H atoms of the type —O—C—H is found from the results of the *CHELP* calculations but not by Mulliken analysis. These H atoms carry either a negative or a very small positive charge. They are, therefore, much more negatively charged than the —C—C—H type H atoms (details are given in the supplementary material).

The molecules pack in columns around the twofold screw axis (Fig. 2). The centroid of the six-atom pyrimidine ring plane (−0.0013, 0.1247, 0.0057) lies almost exactly on the screw axis. There is, therefore, excellent overlap of pyrimidine ring atoms related by the twofold screw axis along the stack, with an interplanar separation of 4.03 Å. The water molecules lie in between the columns of nucleoside molecules and

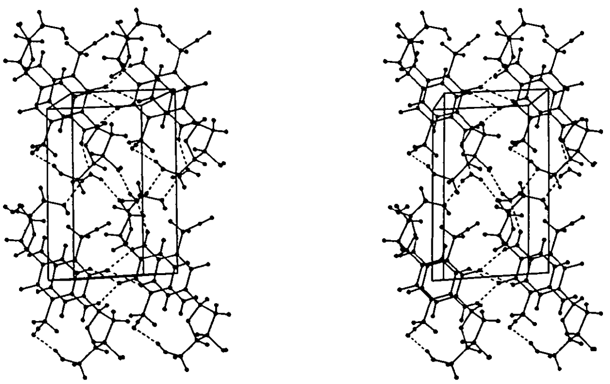

Fig. 2. A stereoscopic packing diagram viewed approximately down the *b* axis. Hydrogen bonds and the short contacts between atoms H(5) and O(2) are shown as dashed lines.

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* It was suggested by a referee that the constraint on rotation around the N(3)—B bond imposed by the hydrogen bond between N(5) and O(5′) may be responsible for the close intramolecular contact between atoms H(1B) and H(1N4). We have, therefore, optimized the structure at two other values of the dihedral angle C(2)—N(3)—B—C(3): −180° (antiperiplanar) and −60° (synclinal). The total energy of the optimized molecule at −60° was very close to that at −75°, the crystal conformation. The total energy of the optimized molecule at −180°, however, was higher than that of the optimized molecule at the crystal conformation by approximately 8.6 kJ (the optimized dihedral angle was −173°). From these, admittedly limited, energy calculations it seems quite likely that the close contact of 2.05 Å observed in the crystal between H(1B) and H(1N4), and the corresponding charges calculated for the optimized molecule in that neighborhood, are intrinsic to the molecule and not a result of atom N(5) participating in a hydrogen bond.

form four hydrogen bonds each, two as donor and two as acceptor, to the sugar and pyrimidine ring atoms in adjacent columns (Table 3). The stacking of the molecules along the twofold screw axis is stabilized by the usual dispersion forces plus one intra-stack hydrogen bond between O(5′) and N(5). There are no short intermolecular distances involving only non-H atoms (Pauling, 1960), but there are some short intermolecular distances involving H atoms (Table 2).

Experimental

The boronated nucleoside was prepared as reported previously (Sood *et al.*, 1989). Crystals were obtained from an enantiomerically pure sample used for an NMR experiment. The sample was dissolved in 100% D_2O at room temperature and concentrated using a rotary evaporator. The evaporation was stopped at the first appearance of small crystals. The sample was then placed in an inert atmosphere and sealed. The sealed NMR tube was covered with aluminium foil and placed in a freezer. Crystals suitable for X-ray analysis appeared after approximately a week.

Crystal data

$C_{10}H_{15}BN_4O_4.H_2O$
$M_r = 284.08$
Monoclinic
$P2_1$
$a = 6.879\ (2)$ Å
$b = 8.215\ (2)$ Å
$c = 11.961\ (2)$ Å
$\beta = 93.3\ (2)°$
$V = 674.8\ (3)$ Å^3
$Z = 2$
$D_x = 1.40$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 6.5–11°$
$\mu = 0.104$ mm^{-1}
$T = 298$ K
Block
0.52 × 0.40 × 0.28 mm
Colorless

Data collection

Siemens $R3m/\mu$ diffractometer
ω scans
Absorption correction: none
2147 measured reflections
2092 independent reflections
1681 observed reflections [$F_o > 6\sigma(F_o)$]

$R_{\rm int} = 0.028$
$\theta_{\rm max} = 30°$
$h = -9 \rightarrow 9$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 16$
2 standard reflections monitored every 48 reflections intensity variation: ±1.8%

Refinement

Refinement on F
$R = 0.0456$
$wR = 0.0511$
$S = 2.06$
1681 reflections
248 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F) + 0.0002F^2]$

$(\Delta/\sigma)_{\rm max} = 0.03$
$\Delta\rho_{\rm max} = 0.27$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.18$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
N(1)	0.8628 (3)	0.8492	0.9097 (2)	0.031 (1)
C(2)	0.8070 (3)	0.8561 (4)	1.0185 (2)	0.030 (1)
O(2)	0.6355 (2)	0.8523 (4)	1.0379 (2)	0.049 (1)
N(3)	0.9525 (3)	0.8659 (3)	1.1037 (2)	0.029 (1)
C(4)	1.1422 (3)	0.8855 (4)	1.0807 (2)	0.028 (1)
N(4)	1.2801 (3)	0.8990 (3)	1.1615 (2)	0.034 (1)
C(5)	1.1912 (4)	0.8927 (5)	0.9671 (2)	0.043 (1)
C(6)	1.0520 (3)	0.8722 (5)	0.8858 (2)	0.041 (1)
B	0.8803 (4)	0.8438 (5)	1.2271 (2)	0.035 (1)
C(3)	0.7730 (4)	1.0061 (4)	1.2614 (2)	0.038 (1)
N(5)	0.6960 (4)	1.1210 (5)	1.2885 (2)	0.059 (1)
C(1′)	0.7077 (3)	0.8178 (4)	0.8192 (2)	0.029 (1)
C(2′)	0.6135 (4)	0.9716 (4)	0.7699 (2)	0.037 (1)
C(3′)	0.7062 (4)	0.9897 (4)	0.6578 (2)	0.033 (1)
O(3′)	0.5819 (4)	1.0632 (3)	0.5732 (2)	0.049 (1)
C(4′)	0.7425 (4)	0.8137 (4)	0.6269 (2)	0.031 (1)
O(4′)	0.7986 (3)	0.7368 (1)	0.7326 (1)	0.033 (1)
C(5′)	0.8967 (5)	0.7828 (4)	0.5445 (3)	0.047 (1)
O(5′)	1.0783 (3)	0.8571 (4)	0.5777 (2)	0.055 (1)
O(1*W*)	0.3471 (3)	0.8906 (3)	0.4111 (2)	0.040 (1)

Table 2. *Selected geometric parameters (Å, °)*

N(1)—C(2)	1.379 (3)	C(4)—N(4)	1.320 (3)
N(1)—C(1′)	1.498 (3)	C(5)—C(6)	1.336 (3)
C(2)—N(3)	1.389 (3)	C(3)—N(5)	1.139 (5)
N(3)—B	1.594 (3)	C(1′)—O(4′)	1.407 (3)
C(4)—C(5)	1.419 (3)	C(3′)—O(3′)	1.421 (3)
B—C(3)	1.589 (5)	C(4′)—O(4′)	1.446 (3)
C(1′)—C(2′)	1.523 (4)	C(5′)—O(5′)	1.427 (4)
C(2′)—C(3′)	1.525 (4)	O(2)···H(5$^{\rm i}$)	2.36 (3)
C(3′)—C(4′)	1.517 (4)	C(3)···H(5″$^{\rm ii}$)	2.87 (4)
C(4′)—C(5′)	1.511 (4)	B···H(5″$^{\rm ii}$)	2.91 (4)
N(1)—C(6)	1.362 (3)	C(3)···H(5′O$^{\rm iii}$)	2.87 (5)
C(2)—O(2)	1.216 (3)	O(2)···C(5$^{\rm i}$)	3.142 (3)
N(3)—C(4)	1.359 (3)		
C(2)—N(1)—C(6)	120.9 (2)	C(2)—N(1)—C(1′)	117.6 (2)
C(6)—N(1)—C(1′)	121.5 (2)	N(1)—C(2)—O(2)	120.3 (2)
N(1)—C(2)—N(3)	117.9 (2)	O(2)—C(2)—N(3)	121.8 (2)
C(2)—N(3)—C(4)	121.1 (2)	C(2)—N(3)—B	115.0 (2)
C(4)—N(3)—B	123.8 (2)	N(3)—C(4)—N(4)	121.3 (2)
N(3)—C(4)—C(5)	118.9 (2)	N(4)—C(4)—C(5)	119.8 (2)
C(4)—C(5)—C(6)	119.4 (2)	N(1)—C(6)—C(5)	121.3 (2)
N(3)—B—C(3)	108.5 (2)	B—C(3)—N(5)	178.4 (3)
N(1)—C(1′)—C(2′)	114.0 (2)	N(1)—C(1′)—O(4′)	106.5 (2)
C(2′)—C(1′)—O(4′)	107.7 (2)	C(1′)—C(2′)—C(3′)	103.4 (2)
C(2′)—C(3′)—O(3′)	113.7 (2)	C(2′)—C(3′)—C(4′)	101.8 (2)
O(3′)—C(3′)—C(4′)	109.4 (2)	C(3′)—C(4′)—O(4′)	104.1 (2)
C(3′)—C(4′)—C(5′)	116.8 (2)	O(4′)—C(4′)—C(5′)	109.6 (2)
C(1′)—O(4′)—C(4′)	109.2 (2)	C(4′)—C(5′)—O(5′)	112.5 (3)

Symmetry codes: (i) $x - 1, y, z$; (ii) $x, y, 1 + z$; (iii) $2 - x, \frac{1}{2} + y, 2 - z$.

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N(4)—H(1N4)···O(1*W*$^{\rm i}$)	0.91 (3)	2.17 (3)	2.994 (3)	151 (3)
N(4)—H(2N4)···O(2$^{\rm ii}$)	0.89 (3)	2.15 (3)	2.954 (3)	150 (3)
O(3′)—H(3′O)···O(1*W*$^{\rm iii}$)	0.71 (5)	2.04 (5)	2.738 (3)	168 (5)
O(5′)—H(5′O)···N(5$^{\rm iv}$)	0.77 (4)	2.16 (4)	2.906 (4)	164 (4)
O(1*W*)—H(1*W*)···O(3′)	0.83 (4)	2.04 (4)	2.832 (4)	159 (4)
O(1*W*)—H(2*W*)···O(5′$^{\rm v}$)	0.77 (4)	2.08 (4)	2.809 (4)	159 (4)

Symmetry codes: (i) $1 + x, y, 1 + z$; (ii) $1 + x, y, z$; (iii) $1 - x, \frac{1}{2} + y, 1 - z$; (iv) $2 - x, y - \frac{1}{2}, 2 - z$; (v) $x - 1, y, z$.

Table 4. *Cytosine ring torsion angles (°) from the X-ray study and the MO calculation, and mean values calculated from entries in the Cambridge Structural Database*[a]

	X-ray study[b]	MO study[b]	Mean[c]
N(1)—C(2)—N(3)—C(4)	6.9 (4)	5.2	0.6 (11)
C(2)—N(3)—C(4)—C(5)	−1.3 (5)	−3.2	0.7 (9)
N(3)—C(4)—C(5)—C(6)	−3.2 (5)	0.4	1.1 (9)
C(4)—C(5)—C(6)—N(1)	1.9 (6)	0.1	0.2 (4)
C(5)—C(6)—N(1)—C(2)	4.0 (5)	2.1	1.1 (8)
C(6)—N(1)—C(2)—N(3)	−8.2 (4)	−4.7	1.4 (13)

References: (*a*) Allen *et al.* (1979); (*b*) this work; (*c*) Taylor & Kennard (1982).

The intensity data were collected at variable scan speeds ranging from 4 to 29° min^{-1} depending on intensity. Stationary backgrounds were counted on both sides of a peak, each for one-half of the scan time. The structure was solved by direct methods and difference Fourier techniques, and refined by blocked-cascade least-squares methods (Sparks, 1961). H atoms were located from a difference Fourier calculation. Non-H atoms were refined with anisotropic and H atoms with isotropic displacement parameters. Calculations were performed on a Data General micro-eclipse desktop model 30 computer. Software used: *SHELXTL* (Sheldrick, 1985) for structure solution, refinement and molecular graphics.

The X-ray data were collected and processed at North Carolina State University, Raleigh, NC. Work at Duke University was supported by the North Carolina Supercomputing Center and by a grant from the American Cancer Society (NP-741) to BRS. We thank Dr Charles Campana of Siemens Industrial Automation for providing Fig. 2.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, torsion angles and charges on —C—C—H and —O—C—H H atoms calculated using Mulliken analysis and *CHELP* have been deposited with the IUCr (Reference: BK1157). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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L-Histidine Methyl Ester Dihydrochloride

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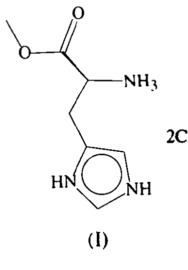
Abstract

The title compound, $C_7H_{13}N_3O_2^{2+}.2Cl^-$, has distances and angles quite similar to those of histidine hydrochloride monohydrate [Donohue & Caron (1964). *Acta Cryst.* **17**, 1178–1180], except for the distances within the ester functionality.

Comment

We have been synthesizing a series of ligands of the form edta(R–aa)$_2$, where R = CH_3 and CH_2CH_3, in which two amino acid esters (R–aa) are amide-linked to an ethylenediaminetetraacetic acid (H_4edta) backbone (Whalen, 1994; Davidson, 1995). During our attempts to make edta(Me–His)$_2$, the solids that were recovered, and recrystallized, after 8 h of reflux proved to be the title compound rather than the desired product.



(I)