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STUDIES ON BREDININ. II
THE MOLECULAR STRUCTURE OF BREDININ

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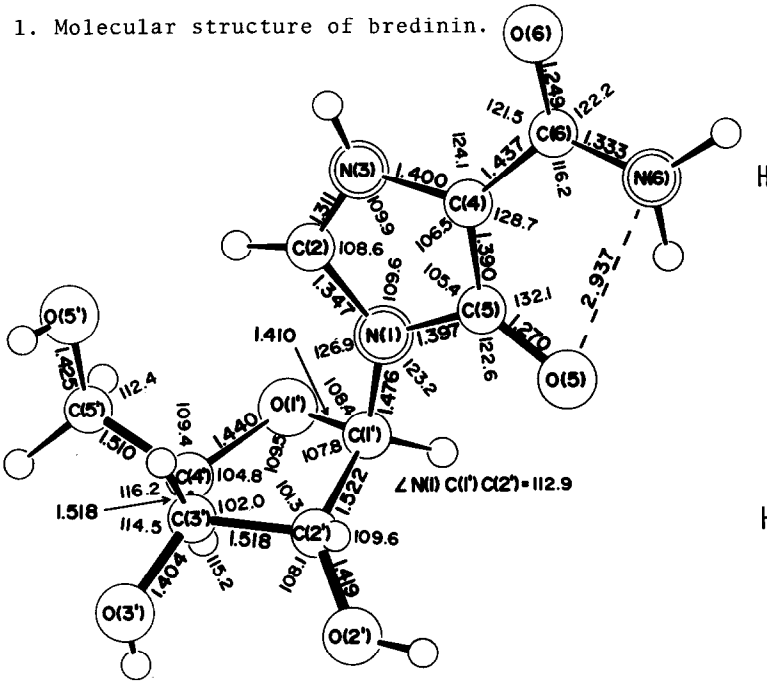
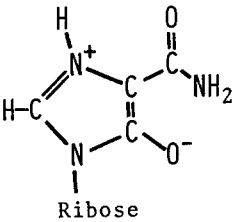
Bredinin, a novel imidazole nucleoside, has been characterized as an immunosuppressant[1,2]. In order to elucidate the chemical and three-dimensional structures of the molecule, we undertook an X-ray crystallographic analysis of its monohydrate crystals ($C_9H_{13}N_3O_6 \cdot H_2O$, F.W.=277.2).

Crystals of suitable quality for an X-ray work were obtained from a water-acetone solution as transparent prisms elongated along the c axis. They belong to the orthorhombic space group $P2_12_12_1$ with a unit cell of dimensions: a= 11.367(1), b=13.998(2), and c=7.478(1) Å. There are four formula units in the cell (D_m=1.49, D_x=1.547 g/cm^3). The intensity data were collected on a Rigaku automatic four-circle diffractometer with LiF-monochromated Mo-Kα radiation. A total of 1209 independent reflections with 2θ less than 50° were measured in the θ-2θ scanning mode, and of those 915 had |F| values greater than three times their standard deviations and were used in the structure analysis.

The structure was solved by an application of the direct method[3]. Phases of 250 reflections with $|E| \geq 1.3$ could be determined and the resulting E map revealed all nineteen non-hydrogen atoms. Initially all the atomic species of the base moiety were treated as carbon for lack of the chemical knowledge, and later the respective species were unambiguously identified by the relative magnitudes of the isotropic temperature factors and the residuals on difference Fourier maps. The structure was refined by block-diagonal least-squares method. Several cycles of the least-squares calculations for the non-hydrogen atoms with anisotropic thermal parameters resulted in a conventional R factor

Fig. 1. Molecular structure of bredinin.





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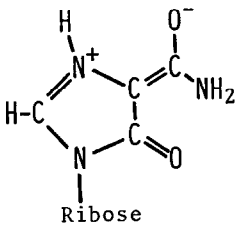

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of 0.067. All the hydrogen atoms of the molecule were found from difference maps, and they were refined with isotropic thermal parameters. The difference maps also indicated the disordered water oxygen atom(O(W') in Table 1), to which a fixed occupancy factor of 0.1 was assigned and refined isotropically. The final R was 0.034. The final atomic coordinates are listed in Table 1.

The molecular structure thus determined, shown in Fig. 1, approves that bredinin is best described as 4-carbamoyl-1-β-D-ribofuranosyl imidazolium-5-olate, 1. The molecule assumes a zwitterion structure; the proton originally bonded to the O(5) atom may be regarded as being transferred to the N(3) atom. The zwitterion structure was also found by an X-ray analysis in the aglycone of bredinin or 4(5)-carbamoyl imidazolium-5(4)-olate.[4] In Fig. 1 are given the bond lengths(in Å) and the bond angles(in deg.) for the non-hydrogen atoms, the estimated standard deviations being about 0.005 Å and 0.4°, respectively. The C-H, N-H, and O-H distances are in the range of 0.97∿1.06 Å(mean 1.01 Å), 0.92∿1.06 Å(mean 0.97 Å), and 0.86∿0.99 Å(mean 0.93 Å), respectively, with the mean estimated standard deviation of 0.04 Å.

The imidazole ring is planar with the root-mean-square deviation of 0.005 Å. The O(5) atom lies on the ring plane, while the atoms, C(6), O(6), N(6), and C(1'), deviate from the plane by 0.21, 0.43, 0.21, and 0.13 Å, respectively. One of the amino hydrogen atoms participates in the intramolecular hydrogen bond between N(6) and O(5). Bond lengths and angles of the imidazole ring may be compared with those found in N-(β-D-ribofuranosyl)-imidazole,[5] 3.

The bonds, N(3)-C(4), C(4)-C(5), and C(5)-N(1), of bredinin are appreciably longer by 0.02∿0.03 Å than those in 3; these results suggest that a valence bond structure 2 contributes considerably in addition to 1. The structure 2 also explains well that the exocyclic bond lengths of C(4)-C(6) and C(5)-O(5) are shorter than the typical single bond lengths expected for $C(sp^2)$-$C(sp^2)$ and $C(sp^2)$-O, respectively, and the C(6)-O(6) length is longer than the C=O double bond length. It is noted that no resonance structures similar to 2 are present in 3. The most remarkable difference in bond angles between bredinin and 3 occurs at ∠C(2)-N(3)-C(4); this is ascribable to the usual effect of the protonated and unprotonated nitrogen atoms to the bond angles.[6]

The ring puckering of the ribose moiety is described as C(3')-endo; the C(3') atom is displaced 0.578 Å from the mean plane of the remaining ring atoms toward the same side as C(5'). The tortional angles ϕ_{OO}[O(1')-C(4')-C(5')-O(5')] and ϕ_{CO}[C(3')-C(4')-C(5')-O(5')] are -62.6° and 55.8°, respectively. Therefore, the conformation about the C(4')-C(5') bond is gauche-gauche. The glycosidic tortional angle χ_{CN}[C(2)-N(1)-C(1')-O(1')] is 24.1°, and thus the conformation is anti. This contrasts with the syn conformation found in 3. Certain bond distances and angles appreciably differ from the average values for β-D-ribose residues having C(3')-endo conformation,[7,8] but most of them lies within the range found for other nucleosides. The largest discrepancy occurs at ∠C(4')-C(3')-O(3') (114.5°), which is 5.6° greater than the average value given in the reference 8.

In the crystals bredinin and the water molecules are linked together by hydrogen bonds to form a three-dimensional network. All the available groups, including the water of crystallization, participate in the hydrogen bonds, their distances(from donor to acceptor atom) being, N(3)-H···O(3')=2.722, N(6)-H···O(6)=3.058, O(5')-H···O(5)=2.675, O(3')-H···O(5')=2.726, O(2')-H···O(W)=2.835, O(W)-H1(W)···O(5)=2.891, and O(W)-H2(W)···O(3')=2.769 Å, with estimated standard deviations of ca. 0.003 Å.

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Table 1. Fractional atomic coordinates. Standard deviations are given in parentheses.

Atom	x	y	z
O(1')	0.3456(2)	0.2268(1)	0.3271(3)
C(1')	0.3I72(3)	0.3003(2)	0.4486(4)
C(2')	0.2134(3)	0.3555(2)	0.3719(5)
C(3')	0.2286(3)	0.3374(2)	0.1732(4)
C(4')	0.2726(3)	0.2350(2)	0.1705(4)
C(5')	0.3423(3)	0.2055(3)	0.0076(5)
O(2')	0.1066(2)	0.3122(2)	0.4273(3)
O(3')	0.1280(2)	0.3536(2)	0.0686(3)
O(5')	0.4411(2)	0.2659(2)	-0.0231(3)
N(1)	0.4225(2)	0.3603(2)	0.4749(3)
C(2)	0.5132(3)	0.3712(2)	0.3607(5)
N(3)	0.5946(2)	0.4228(2)	0.4389(4)
C(4)	0.5585(3)	0.4472(2)	0.6119(4)
C(5)	0.4470(3)	0.4081(2)	0.6346(4)
C(6)	0.6337(3)	0.4905(2)	0.7432(4)
O(6)	0.7396(2)	0.5072(2)	0.7114(3)
N(6)	0.5853(2)	0.5081(3)	0.9022(4)
O(5)	0.3759(2)	0.4091(2)	0.7657(3)
O(W)	0.1244(2)	0.4334(2)	0.7298(4)
H(C1')	0.301(2)	0.275(2)	0.570(4)
H(C2')	0.210(3)	0.428(2)	0.402(4)
H(C3')	0.290(2)	0.383(2)	0.124(4)
H(C4')	0.203(3)	0.193(2)	0.189(4)
H1(C5')	0.374(3)	0.141(2)	0.031(4)
H2(C5')	0.285(3)	0.203(2)	-0.104(5)
H(O2')	0.088(3)	0.347(3)	0.539(5)
H(O3')	0.072(3)	0.313(2)	0.080(4)
H(O5')	0.416(3)	0.315(2)	-0.096(4)
H(C2)	0.516(3)	0.344(2)	0.242(4)
H(N3)	0.663(2)	0.444(2)	0.385(4)
H1(N6)	0.505(2)	0.497(2)	0.926(4)
H2(N6)	0.634(3)	0.529(3)	1.017(5)
H1(W)	0.200(4)	0.422(3)	0.733(5)
H2(W)	0.092(3)	0.406(3)	0.839(6)
O(W')*	0.037(2)	0.404(2)	0.721(3)

* Hydrogen atoms bonded to the lower weight O(W') atom were not found.