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THE CRYSTAL STRUCTURE OF DIAZOMETHYL β-D-GALACTOPYRANOSYL KETONE

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ABSTRACT

The title compound ($C_8H_{12}N_2O_6$) crystallizes in the orthorhombic space group $P2_12_12_1$ ($Z = 4$), with $a = 4.871(1)$, $b = 11.136(2)$, $c = 18.301(2)$ Å. The structure was solved by the multi-solution technique and refined by full-matrix least-squares to a final R-index of 0.042. The compound adopts the $^4C_1$(D) conformation. Bond lengths in the diazoacetyl group are consistent with the presence of a zwitterion.

INTRODUCTION

The title compound (**1**) has been shown to be an irreversible inhibitor (suicide substrate) of an acidic β-D-galactosidase from *Aspergillus oryzae*[1]. This structural analysis was undertaken to study the effect of replacing OH-1 of a β-D-galactopyranose by a diazoacetyl group, the carbonyl carbon atom being attached to C-1, and to compare the molecular structure of the diazoacetyl group with that of that of 3-*O*-diazoacetyl-L-serine, which is another organic structure containing this substituent.

EXPERIMENTAL

The synthesis of the title compound was reported by Myers and Lee[2]. Crystals were grown by evaporation from ethanol–water. X-Ray intensity data were collected on an Enraf–Nonius CAD4 diffractometer, using Ni-filtered CuKα radiation (λ 1.5418 Å). Using a crystal measuring 0.8 × 0.7 × 0.5 mm, 1254 unique re-

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flections were collected up to a 2θ limit of 140°. Of these, 1155 reflections with $I/\sigma(I)>2$ were considered observed, and used for the structure analysis. The data were corrected for decay (maximum of 8%) by monitoring three reflections every two hours during data collection. An empirical absorption-correction was applied (maximum of 4%) using a ϕ curve. The data were also corrected for Lorentz and polarization effects.

The structure was solved by the multi-solution technique using the program MULTAN[3]. All 16 nonhydrogen atoms were located from the phase set with the highest figure of merit. These 16 atoms were refined to convergence by full-matrix least-squares. All hydrogen atoms were subsequently located from difference-Fourier maps. The structure was refined to a final R-index of 0.042 using anisotropic thermal parameters for the nonhydrogen atoms and fixed isotropic thermal

TABLE I

FRACTIONAL POSITIONAL PARAMETERS[a] FOR ALL ATOMS OF DIAZOMETHYL β-D-GALACTOPYRANOSYL KETONE (**1**)

Atom	x	y	z	B_{eq}[b]
C-1	8058(5)	3717(2)	1446(1)	2.30(4)
C-2	8279(5)	2444(2)	1111(1)	2.32(6)
O-2	7219(4)	2459(2)	388(1)	3.22(4)
C-3	6645(5)	1591(2)	1585(1)	2.44(6)
O-3	6975(5)	393(2)	1315(1)	3.40(6)
C-4	7580(5)	1657(2)	2379(1)	2.41(6)
O-4	10350(4)	1255(1)	2451(1)	2.84(3)
C-5	7441(5)	2956(2)	2639(1)	2.26(6)
O-5	9083(4)	3711(1)	2178(1)	2.38(3)
C-6	8523(7)	3080(2)	3410(1)	2.82(6)
O-6	8042(4)	4241(2)	3711(1)	2.98(3)
C-A	9742(6)	4620(2)	1021(1)	2.58(6)
O-A	12174(5)	4786(2)	1147(1)	4.69(6)
C-B	8317(7)	5284(3)	481(2)	3.67(7)
N-1	9822(5)	6040(2)	94(1)	3.12(6)
N-2	11246(6)	6657(2)	−200(1)	4.08(7)
H-1	637(8)	397(3)	142(2)	4.0
H-2	1031(7)	227(3)	109(2)	4.0
H-O-2	845(7)	239(3)	9(2)	4.0
H-3	459(8)	177(3)	157(2)	4.0
H-O-3	517(8)	11(3)	133(2)	4.0
H-4	621(7)	129(3)	262(2)	4.0
H-O-4	1021(7)	71(3)	252(2)	4.0
H-5	554(7)	316(3)	263(2)	4.0
H-1-6	1048(8)	293(3)	344(2)	4.0
H-2-6	749(7)	248(3)	374(2)	4.0
H-O-6	992(7)	458(3)	369(2)	4.0
H-B	629(7)	528(3)	40(2)	4.0

[a] Values are multiplied by 10^4 for non-hydrogen atoms and 10^3 for hydrogen atoms.

[b] $B_{eq} = {}^4/_3 \sum_i \sum_j a_i \cdot a_j \beta_{ij}$, where a_i values are cell constants in direct space.

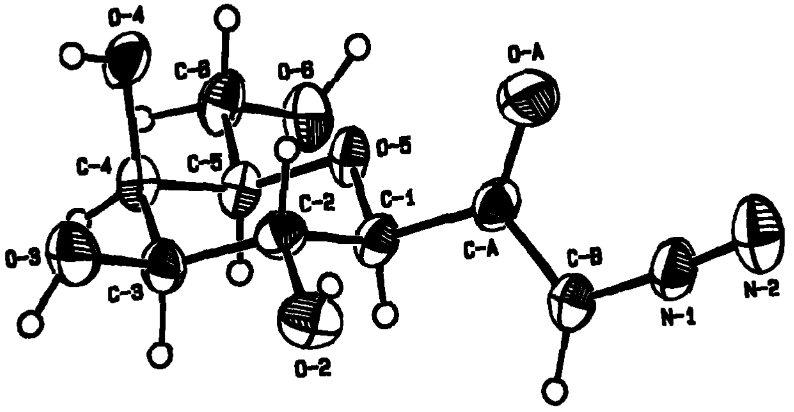

Fig. 1. ORTEP drawing of diazomethyl β-D-galactopyranosyl ketone (1), showing nonhydrogen atoms with 50% thermal-probability ellipsoids and hydrogen atoms as spheres of arbitrary size.

parameters of 4.0 Å for the hydrogen atoms. In the final cycle of refinement, the maximum shift:error ratios were 0.01:1.00 and 0.16:1.00 for nonhydrogen and hydrogen atoms, respectively. The weight of each reflection during refinement was proportional to $1/[\sigma^2(F) + (0.02F_o)^2]$, where F_o is the observed structure factor, and $\sigma(F)$ is the standard deviation. The atomic-scattering factors for the nonhydrogen atoms were taken from Cromer and Waber[4] and those for hydrogen atoms are from Stewart *et al.*[5].

RESULTS AND DISCUSSION

Atomic positional parameters are presented in Table I. Anisotropic thermal parameters and lists of observed and calculated structure factors are given as supplementary material*. An ORTEP drawing[6] indicating atom numbering is shown in Fig. 1. Bond lengths and angles for nonhydrogen atoms are given in Table II. The average (and standard deviation) for the C–C bond lengths of the pyranosyl unit is 1.525(13) Å; the average C–O bond length is 1.428(5) Å. These values lie within the expected range for pyranoid structures[7,8], except for the C-1–C-2 bond-length of 1.548(3) Å, which is significantly longer than the average. This lengthening may be related to the presence of the diazoketo substitution at the anomeric carbon atom, where the carbonyl carbon atom is attached to C-1.

The structure of 3-*O*-diazoacetyl-L-serine (azaserine) is the only crystallographic investigation of a similar diazo-substituted organic compound previously reported in the literature[9]. The bond lengths used for azaserine are the average values for the two independent molecules determined at 0°. The structure of

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*A table of anisotropic thermal parameters and a list of observed and calculated structure factors have been deposited with, and may be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/377/ *Carbohydrate Res.*, 168 (1987) 7–13.

TABLE II

BOND LENGTHS[a] (Å) AND ANGLES (DEGREES) FOR DIAZOMETHYL β-D-GALACTOPYRANOSYL KETONE (1)

Bond lengths					
C-1–C-2	1.548	C-1–O-5	1.430	C-1–C-A	1.513
C-2–O-2	1.420	C-2–C-3	1.513	C-3–O-3	1.432
C-3–C-4	1.525	C-4–O-4	1.428	C-4–C-5	1.524
C-5–O-5	1.435	C-5–C-6	1.513	C-6–O-6	1.425
C-A–O-A	1.221	C-A–C-B	1.416	C-B–N-1	1.322
N-1–N-2	1.115				

Bond angles			
C-2–C-1–O-5	110.0	C-2–C-1–C-A	111.6
O-5–C-1–C-A	107.2	C-1–C-2–O-2	109.4
C-1–C-2–C-3	108.1	O-2–C-2–C-3	110.5
C-2–C-3–O-3	109.1	C-2–C-3–C-4	111.0
O-3–C-3–C-4	109.9	C-3–C-4–O-4	110.8
C-3–C-4–C-5	109.3	O-4–C-4–C-5	108.1
C-4–C-5–O-5	110.4	C-4–C-5–C-6	111.2
O-5–C-5–C-6	107.5	C-5–C-6–O-6	112.7
C-1–O-5–C-5	111.0	C-1–C-A–O-A	122.0
C-1–C-A–C-B	116.1	O-A–C-A–C-B	121.9
C-A–C-B–N-1	115.8	C-B–N-1–N-2	174.9

[a] Estimated errors for the bond lengths are 0.03 Å, and for bond angles, 0.2°.

azaserine differs from that of **1** in that it is an ester having an oxygen atom inserted between the diazoacetyl group and the rest of the molecule. In both structures, the diazo moiety exists as a zwitterion with the terminal nitrogen atom (N-2) negatively charged and the adjacent nitrogen atom (N-1) positively charged. The bonding character of the diazoacetyl group can be described as a resonance structure derived from the two canonical structures shown in Fig. 2a. A comparison of the geometry of the diazoacetyl moiety in **1** and azaserine (see Fig. 2b) suggests that the two resonance-forms depicted contribute in different proportions for each molecule. The C-A–O-A carbonyl bond-length of 1.221(4) Å in **1** is significantly longer than the corresponding bond-length in azaserine of 1.202(7) Å, and the C-A–C-B bond-length of 1.416(4) Å is significantly shorter than the corresponding distance of 1.430(7) Å. The C-B–N-1 distance of 1.322(4) Å in **1** is slightly longer than the 1.312(9) Å average value for azaserine, and the N-1–N-2 bond-length of 1.115(3) Å is slightly shorter than the azaserine values of 1.128(9) Å. These differences in the bond lengths are consistent with different partial resonance contributions from the two canonical structures depicted in Fig. 2, with structure II contributing to a greater extent in **1** than in azaserine. In contrast, structure I is more predominant in azaserine than in **1**.

The average bond-angle between nonhydrogen atoms in the pyranosyl unit is 110.0(13)°. The exocyclic bond-angle O-5–C-1–C-A of 107.2(2)° agrees with the mean bond-angle of 107.0(8)° for anomeric substituents in the equatorial position[10]. The 111.0(2)° angle about O-5 is slightly narrower than the mean of 112.6(20)° for

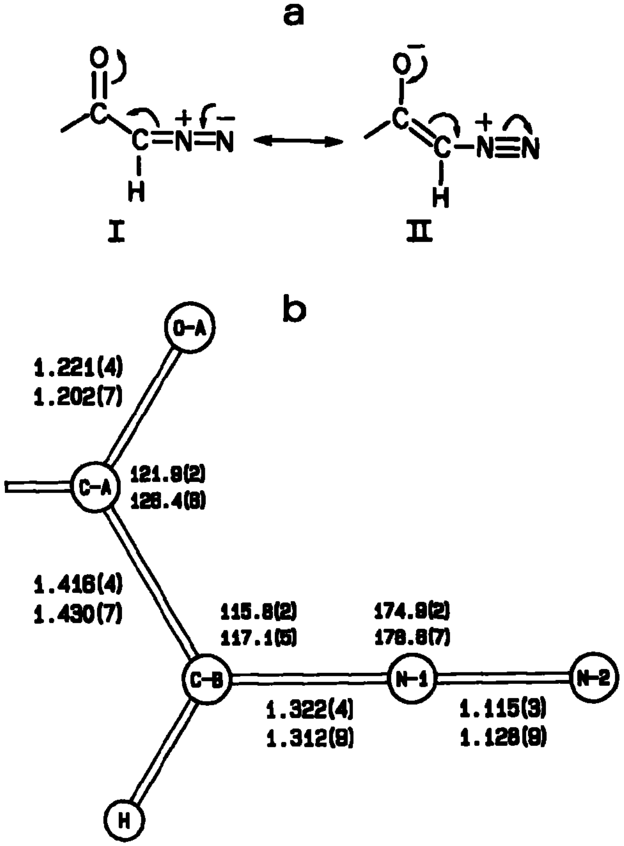

Fig. 2. (a) The two possible resonance-structures representing the resonance states of the diazoacetyl moiety. (b) Comparison of the bond lengths and angles for 1 (top values) and azaserine (bottom).

pyranosides having an equatorial anomeric group[7,8]. The C-1–C-A–C-B bond-angle of 116.1(3)° is significantly wider than the corresponding O–C–C angle in azaserine, which has an average value of 109.9(6)°. The C-B–N-1–N-2 angle of 174.9(2)° is significantly less linear than the average azaserine angle of 178.6(7)°. Interestingly, the increased single-bond character of the C-B–N-1 bond and the triple bond character of the N-1–N-2 bond apparently result in bending at N-1.

The ring puckering is quantitatively defined[11] by $Q = 0.593(4)$ Å, $\theta = 3.0(3)°$, $\phi = 25(6)°$, which is very close to that of the ideal chair conformation. The compound is in the usual *gauche–trans* orientation, with the O-5–C-5–C-6–O-6 torsion-angle equal to 68.1(3)°, and the C-4–C-5–C-6–O-6 torsion-angle equal to −171.0(3)°. The C-1–C-A–C-B–N-1 torsion-angle is *trans*, with a value of −177.7(4)°, which is in the same domain as the average value of +177(2)° observed for azaserine.

A molecular-packing diagram is shown in Fig. 3. All available protons on oxygen atoms participate in hydrogen bonding (see Table III). Hydrogen bonding

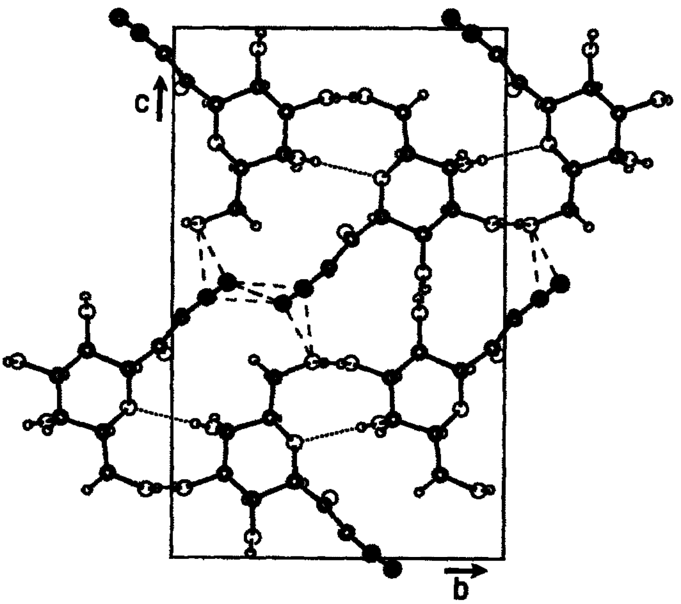

Fig. 3. Crystal-packing diagram viewed down the *a* axis, with the *b* axis horizontal and *c* vertical. Hydrogen bonds are shown with dotted lines and intermolecular close contacts involving the diazo group are shown with dashed lines. The carbon atoms are drawn with thick borders, oxygen atoms have thin borders, and nitrogen atoms are blackened.

TABLE III

LIST OF HYDROGEN-BONDING INTERACTIONS IN DIAZOMETHYL β-D-GALACTOPYRANOSYL KETONE (**1**)

Atoms		*Symmetry*[a]				*Distances (Å)*			*Angle (°)*
A-H···B		N	X	Y	Z	*A-H*	*H···B*	*A···B*	*A-H···B*
O-2	H-O-2···O-2	3	0	0	0	0.81	2.04	2.821	160
O-3	H-O-3···O-6	4	1	−1	0	0.93	1.84	2.761	167
O-4	H-O-4···O-5	4	2	−1	0	0.62	2.32	2.926	165
O-6	H-O-6···O-3	4	2	0	0	0.99	1.76	2.746	171

[a]Symmetry codes: *N* = 3: 1/2 + *x*, 1/2 − *y*, −*z*; *N* = 4: −*x*, 1/2 + *y*, 1/2 − *z*.

between O-5 and a symmetry-related O-4, and between O-3 and O-6, creates two infinite hydrogen-bonded chains along the *b* axis, thus simulating a quasi-polysaccharide structure. These molecular chains are cross-linked in the *c* direction by hydrogen bonds between two symmetry-related O-2 atoms, and, in the *a* axial direction, by hydrogen bonds between O-3 and O-6. There is no hydrogen bonding associated with the diazo group. However, the nitrogen atoms of symmetry-related molecules are in close proximity. The N-2 · · · N-1 and N-2 · · · N-2 distances are 3.106(3) and 3.161(3) Å, respectively. The nitrogen atoms also make short contacts with neighboring oxygen atoms: N-1 · · · O-6, 2.907(3); N-2 · · · O-6, 3.055(3);

and N-2 · · · O-3, 3.082(3) Å. These short intermolecular contacts suggest potential dipole–dipole and monopole–dipole interactions. Similar short contacts are also observed in azaserine.

CONCLUSION

This description of the crystal structure of diazomethyl β-D-galactopyranosyl ketone, a suicide substrate for an acidic β-D-galactosidase[1], and a potential photoaffinity labeling molecule[2], is the first report of a diazoacetyl-substituted carbohydrate structure.

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