Acta Cryst. (1996). C52, 1781–1784

(1*R*,2*R*)-4,4-Dimethylpyrazolidine-3,5-dione-α-D-pyranosyl-2-deoxyriboside

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(*Received 22 February 1996; accepted 1 April 1996*)

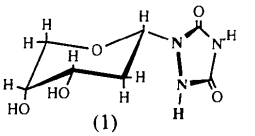
Abstract

The first example of a crystalline pyrazolidinedione nucleoside has been synthesized from the reaction of 2-deoxy-D-ribose with 4,4-dimethylpyrazolidine-3,5-dione and characterized by X-ray crystallography as a single α-pyranoside diastereomer [IUPAC name: 1-(2-deoxy-α-D-*erythro*-pentopyranosyl) 1(*R*),2(*R*)-4,4-dimethylpyrazolidine-3,5-dione], $C_{10}H_{16}N_2O_5$. Although the pyrazolidinedione ring is essentially planar, the two hydrazidic N atoms are pyramidal and chiral, their respective pyranosyl and H-atom substituents being *trans-R,R* configured. The intermolecular hydrogen bonding involves pyranose–pyranose and pyranose–pyrazolidinedione interactions. Each molecule is linked *via* six hydrogen bonds to four surrounding molecules in which the pyrazolidinedione hydrazidic N(H) atom is a donor and its adjacent carbonyl O atom is an acceptor, and the pyranose hydroxylic O atoms are donors as well as acceptors. The second carbonyl O atom has no hydrogen-bonding interactions with OH or NH, but exhibits a weak C—H···O intermolecular interaction with the pyranose ring. The pyranose ring O atom does not participate in hydrogen bonding. Substituting the OH groups with OD and the NH with ND resulted in no measurable changes in the structure (within error), including the hydrogen-bonding parameters.

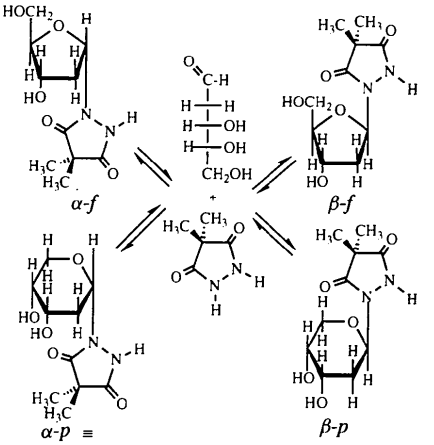
Comment

We recently reported the X-ray structure of the first example of crystalline urazole nucleoside, (1*R*,2*R*)-urazole-α-D-pyranosyl-2-deoxyriboside, (1) (Robinson, Meyers, Kolb & Colloton, 1996). This crystalline structure was unexpected because the deoxyribose moiety had the rare α-pyranose skeleton, but was more unusual because the urazole moiety was chiral by virtue of its two pyramidal hydrazidic N atoms which were exclusively *R,R* configured, although the imidic N atom was trigonal planar. Thus, while the chirality of the deoxyribose substrate could have led to the formation of both (1) and its diastereomer, the only crystalline nucleoside observed was diastereomer (1). These combined findings have a great significance in prebiotic chemistry. Such nucleosides could be incorporated into pyranose RNA, which many believe could have been the ancestral RNA (Pitsch, Wenderborn, Jaun & Eschenmoser, 1993).

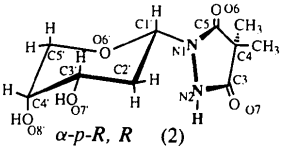
To broaden the scope of this investigation, it was necessary to learn if analogous nucleosides could be obtained similarly with various urazole analogs. Treating a carbon analog of urazole, 4,4-dimethylpyrazolidine-3,5-dione, with 2-deoxy-D-ribose in aqueous solution provided a mixture of nucleosides identified by NMR as four isomeric 4,4-dimethylpyrazolidine-3,5-dione 2-deoxyribosides, α-*f*, β-*f*, α-*p* and β-*p*, as illustrated below. After a number of days crystals separated from the reaction solution. The ^{1}H NMR spectrum exhibited splitting patterns of the deoxyribose moiety resembling those of (1), but could not determine the geometry of the pyrazolidinedione moiety or if it possessed chirality and, therefore, if the crystals represented a single diastereomer and, if so, which one.



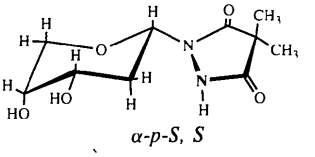
(1)



α-*f* β-*f* α-*p* ≡ β-*p*



α-*p*-*R*, *R* (2)



α-*p*-*S*, *S*

X-ray diffraction identified these crystals as the single diastereomer (1*R*,2*R*)-4,4-dimethylpyrazolidine-3,5-dione-α-D-pyranosyl-2-deoxyriboside, (2), the first example of a crystalline pyrazolidinedione nucleoside and, like its crystalline urazole counterpart, (1), a rare example of a pyranose nucleoside. Fig. 1 shows the molecular structure of (2) and its atom-numbering scheme. The general structure of (2) closely resembles that of (1), the differences emanating from the presence of the imidic trigonal planar N4 atom of (1) giving rise to full resonance involving this atom with both C=O groups.

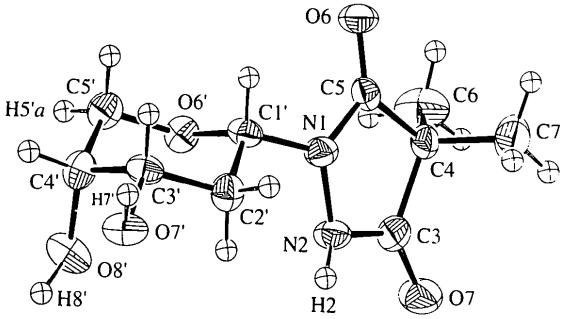


Fig. 1. Molecular structure and atom-numbering scheme for (2) with displacement ellipsoids at the 50% probability level. H atoms are shown as isotropic spheres of arbitrary radii.

The pyrazolidinedione ring of (2) is essentially planar, the mean deviation from planarity being 0.045 Å. The edge-on view of this ring (Fig. 2) clearly shows its stereochemistry. The *R*,*R* chirality of the pyramidal N1, N2 atoms arises from the *trans* juxtaposition of C1′ of the deoxyribose ring and H2, which imposes torsion angles of −56 (3) for C1′—N1—N2—H2, −161.8 (3) for C1′—N1—C5—C4, and −143 (3)° for H2—N2—C3—C4. Near coplanarity of the carbonyl O7 atom with its ring is shown by the torsion angles of 177.1 (4) for O7—C3—C4—C5 and 175.1 (4)° for N1—N2—C3—O7. Ring coplanarity of the carbonyl O6 atom is substantially less, the torsion angles being −169.7 (3) for O6—C5—C4—C3 and 166.8 (3)° for N2—N1—C5—O6.

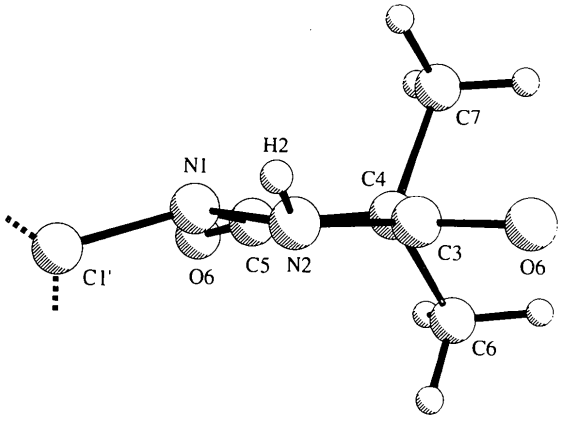


Fig. 2. Edge-on view showing the stereochemistry of the pyrazolidinedione moiety of crystalline (2).

The data in Table 3 show that intermolecular hydrogen bonding involves pyranose–pyranose and pyranose–pyrazolidinedione interactions. Each molecule is linked *via* six hydrogen bonds to four surrounding molecules in which the pyrazolidinedione hydrazidic N2 atom is a donor and its carbonyl O7 atom is an acceptor, while the pyranose hydroxylic O7′ and O8′ atoms are donors as well as acceptors. The carbonyl O6 atom, which hydrogen bonds only with the imidic N4(H) in the urazole nucleoside (1), is not involved in any such way in (2) which is devoid of an N4 atom. However, the possibility of a weak C5′—H5′*a*···O6 intermolecular interaction was noted in crystalline (2) (*cf.* Glusker, Lewis & Rossi, 1994). The O6′ atom in the pyranose ring does not participate in hydrogen bonding with N—H or O—H, a situation we also observed in (1) and which has been reported for ribofuranosides (Birnbaum, Blonski & Hruska, 1983).

The X-ray structure of unsubstituted pyrazolidine-3,5-dione, reported by Fritsch, Zinner, Beimel, Mootz & Wunderlich (1986), shows that this ring, like that of (2), is planar. No torsion angles were reported, but from the parameters given we calculated a torsion angle of 5 (2)° for H1—N1—N2—H2 showing that these hydrazidic N atoms, unlike those of (2), are essentially trigonal planar and H1 and H2 lie in the ring plane. X-ray studies of 1-phenyl- and 1,2-diphenyl-4-*n*-butylpyrazolidine-3,5-dione (Singh & Vijayan, 1977; Paradies, 1987; *cf.* Stoltz, Oliver, Wessels & Chalmers, 1991) showed that the phenyl ring of the former is appended to a trigonal N atom and is coplanar with the pyrazolidine ring, while the two phenyl rings of the latter are appended to pyramidal N atoms, are nearly perpendicular to the pyrazolidine ring and their *trans* juxtaposition imposes dihedral angles with the pyrazolidine ring of 37 and 28°, respectively. Izydore, Bernal-Ramirez & Singh (1990) reported the X-ray structures of 1-acetyl- and 1,2-diacetyl-4,4-diethylpyrazolidine-3,5-dione, whose rings are planar. Hydrazidic N1 of the monoacetyl compound is trigonal planar, its ring-acetyl dihedral angle being only 7.2°, but hydrazidic N1 and N2 of the diacetyl compound are pyramidal, the acetyl groups being *trans* to each other imposing ring–acetyl dihedral angles of 37.5 and 23.3°, respectively. Izydore, Bernal-Ramirez & Singh (1990) associate the trigonality of N1 of the monoacetyl compound with N-acetyl conjugation, which, they report, is not exhibited in the diacetyl compound because these groups are 'twisted out of conjugation'. In comparing the hybridization of the hydrazidic N atoms and associated geometries of (2) and other crystalline pyrazolidine-3,5-diones with those of the unsubstituted parent compound, these disparate data suggest that substituent conjugation with an N atom, intermolecular hydrogen bonding and crystal packing must be considered together as influential factors.

The exclusive formation of only the *R,R* crystalline diastereomer of D-2-deoxyribopyranisides (2) as well as (1) is a matter of concern, especially in view of the fact that these two nucleosides differ substantially in their intermolecular hydrogen-bonding patterns. Whether these *R,R* diastereomers are the sole products of asymmetric induction, the poorly soluble kinetic products or the lesser soluble of the equilibrating products is a matter currently under study.

The crystalline nucleoside in which the O—H and N—H groups of (2) were replaced by O—D and N—D, respectively, was also prepared. Microanalysis and comparative IR spectral analysis assured the complete substitution of these H atoms by D atoms. The crystal structure of the deuterated nucleoside and that of (2) were identical, within error. Thus, we conclude that for this compound any structural changes which may have been brought about by these D/H exchanges, including hydrogen-bonding differences, are immeasurable by routine X-ray structural analysis techniques.

Experimental

In a manner analogous to that reported for the preparation of 4,4-diethylpyrazolidine-3,5-dione (Gillis & Izydore, 1969), treatment of diethyl dimethylmalonate (Aldrich) with hydrazine hydrate (Aldrich) provided 4,4-dimethylpyrazolidine-3,5-dione, mp 530–532 K (from acetone); lit. mp 530 K (Bausch *et al.*, 1991), 530–533 K (Zinner & Böse, 1970). A mixture of this product (128 mg; 1 mmol) and 2-deoxy-D-ribose (134 mg; 1 mmol) in water (2.5 ml) was vigorously agitated. A clear solution, pH was 4.2, was obtained within about 10 min. Samples (evaporated and dried) monitored by ^{1}H and ^{13}C NMR (D_2O solution) several times over a period of days contained four isomeric 4,4-dimethylpyrazolidine-3,5-dione 2-deoxyribosides: α-*f*, β-*f*, α-*p* and β-*p*. After 10 days the reaction mixture contained a mass of well formed crystals which were isolated by filtration. Several recrystallizations from hot water provided crystals suitable for X-ray diffraction. Mp 483–485 K (dec.). Analysis calculated for $C_{10}H_{16}N_2O_5$: C 49.18, H 6.60, N 11.47; found: C 49.04, H 6.61, N 11.47. The X-ray study showed these crystals to be the *R,R*-α-*p*-2-deoxyriboside, (2). The same reaction with 2-deoxyribose carried out in D_2O provided the crystalline nucleoside in which the H atoms of the OH and NH groups were replaced by D. Analysis calculated for $C_{10}H_{13}D_3N_2O_5$: C 48.57, H 5.30, D 2.44, N 11.33; found: C 48.56, 48.55, H 5.22, 5.30, D 2.11, 2.16, N 11.23, 11.06.

Crystal data

$C_{10}H_{16}N_2O_5$	Mo $K\alpha$ radiation
M_r = 244.25	λ = 0.71069 Å
Orthorhombic	Cell parameters from 24 reflections
$P2_12_12_1$	θ = 10.1–11.2°
a = 9.802 (7) Å	μ = 0.11 mm^{-1}
b = 21.172 (5) Å	T = 296 K
c = 5.504 (5) Å	Platy fragment
V = 1142 (2) Å^3	0.41 × 0.37 × 0.10 mm
Z = 4	Colorless
D_x = 1.420 Mg m^{-3}	
D_m not measured	

Data collection

Rigaku AFC-5S diffractometer	1655 observed reflections [$I > \sigma(I)$]
ω scans (rate 3° min^{-1} in ω, 3 reps. maximum)	R_{int} = 0.049
Absorption correction:	θ_{max} = 25°
ψ-scans (North, Phillips & Mathews, 1968)	h = 0 → 11
T_{min} = 0.94, T_{max} = 1.00	k = 0 → 25
2214 measured reflections	l = −6 → 6
2191 independent reflections	3 standard reflections monitored every 150 reflections
	intensity decay: −0.2%

Refinement

Refinement on F	$\Delta\rho_{max}$ = 0.33 e Å^{-3}
R = 0.058	$\Delta\rho_{min}$ = −0.31 e Å^{-3}
wR = 0.048	Extinction correction: none
S = 1.35	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.3.1)
1655 reflections	
157 parameters	
H-atom parameters not refined (riding, C—H 0.95 Å) except H2 (only coordinates refined), and H7′ & H8′ (map positions)	Absolute configuration: determined from the known absolute chirality of the D-2-deoxyribopyranosyl moiety.
$w = 4F_o^2/\sigma^2(F_o^2)$	
$(\Delta/\sigma)_{max}$ = 0.0001	

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

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

	x	y	z	U_{eq}
O6	0.2683 (2)	−0.14304 (12)	−0.0420 (5)	0.0374 (9)
O7	0.6807 (3)	−0.18058 (13)	0.3757 (5)	0.0516 (10)
O6′	0.4188 (2)	0.00173 (11)	0.0606 (4)	0.0311 (8)
O7′	0.6365 (2)	0.08004 (11)	−0.5190 (4)	0.0366 (9)
O8′	0.6016 (3)	0.10399 (11)	−0.0084 (4)	0.0408 (9)
N1	0.4834 (3)	−0.10046 (14)	−0.0405 (6)	0.0320 (10)
N2	0.5997 (3)	−0.10746 (14)	0.1118 (6)	0.0350 (11)
C3	0.5913 (4)	−0.16052 (17)	0.2413 (6)	0.0337 (12)
C4	0.4544 (4)	−0.19169 (15)	0.1905 (6)	0.0288 (11)
C5	0.3865 (4)	−0.14408 (15)	0.0249 (6)	0.0275 (11)
C6	0.3712 (5)	−0.2029 (2)	0.4182 (7)	0.0573 (17)
C7	0.4807 (5)	−0.2535 (2)	0.0540 (9)	0.0603 (16)
C1′	0.4518 (4)	−0.03924 (16)	−0.1377 (6)	0.0300 (12)
C2′	0.5656 (4)	−0.01262 (17)	−0.2931 (6)	0.0323 (12)
C3′	0.5265 (4)	0.05274 (17)	−0.3834 (6)	0.0286 (11)
C4′	0.4892 (4)	0.09436 (17)	−0.1693 (6)	0.0320 (11)
C5′	0.3774 (4)	0.06259 (16)	−0.0263 (6)	0.0347 (12)
H2	0.678 (4)	−0.0945 (17)	0.045 (7)	0.0419

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

O6—C5	1.216 (4)	N2—C3	1.333 (4)
O7—C3	1.224 (4)	C3—C4	1.521 (5)
O6′—C1′	1.431 (4)	C4—C5	1.513 (5)
O6′—C5′	1.433 (4)	C4—C6	1.514 (5)
O7′—C3′	1.433 (4)	C4—C7	1.531 (5)
O8′—C4′	1.428 (4)	C1′—C2′	1.514 (5)

N1—N2	1.423 (4)	C2′—C3′	1.520 (5)
N1—C5	1.373 (4)	C3′—C4′	1.516 (5)
N1—C1′	1.436 (4)	C4′—C5′	1.508 (5)
C1′—O6′—C5′	110.8 (2)	O6—C5—N1	124.6 (3)
N2—N1—C5	109.2 (3)	O6—C5—C4	127.8 (3)
N2—N1—C1′	119.1 (3)	N1—C5—C4	107.6 (3)
C5—N1—C1′	123.8 (3)	O6′—C1′—N1	108.2 (3)
N1—N2—C3	110.7 (3)	O6′—C1′—C2′	111.8 (3)
O7—C3—N2	124.9 (4)	N1—C1′—C2′	112.8 (3)
O7—C3—C4	126.4 (3)	C1′—C2′—C3′	109.8 (3)
N2—C3—C4	108.8 (3)	O7′—C3′—C2′	110.4 (3)
C3—C4—C5	102.1 (3)	O7′—C3′—C4′	110.6 (3)
C3—C4—C6	113.0 (3)	C2′—C3′—C4′	109.6 (3)
C3—C4—C7	108.2 (3)	O8′—C4′—C3′	112.3 (3)
C5—C4—C6	111.5 (3)	O8′—C4′—C5′	107.5 (3)
C5—C4—C7	110.3 (3)	C3′—C4′—C5′	108.8 (3)
C6—C4—C7	111.3 (3)	O6′—C5′—C4′	111.7 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O7′^{i}	0.89 (4)	1.88 (4)	2.746 (4)	163 (4)
O7′—H7′···O8′^{ii}	0.98	1.83	2.763 (4)	157
O8′—H8′···O7^{iii}	1.07	1.74	2.755 (5)	155
C5′—H5′a···O6^{iv}	0.95	2.55	3.471 (5)	165

Symmetry codes: (i) $\frac{3}{2}-x, -y, \frac{1}{2}+z$; (ii) $x, y, z-1$; (iii) $\frac{3}{2}-x, -y, z-\frac{1}{2}$; (iv) $\frac{1}{2}-x, -y, \frac{1}{2}+z$.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *TEXSAN LS*. Molecular graphics: *TEXSAN ORTEP* (Johnson, 1965). Software used to prepare material for publication: *TEXSAN FINISH*; *PLATON* (Spek, 1990).

Special thanks are due Jim Lenke, Director of the Microanalysis Laboratory of the University of Illinois, for carrying out the microanalyses and utilizing the special methodology required for determining deuterium and hydrogen selectively. Thanks are expressed by PAC for a NASA undergraduate research scholarship administered through the Wisconsin Space Grant Consortium, and for a University of Wisconsin-Parkside scholarship. CYM is grateful to Southern Illinois University-Carbondale for supporting this research through Distinguished Professorship research funding.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: FG1174). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1996). C**52**, 1784–1787

1-(*p*-Methoxyphenyl)-2-methyl-4-nitroimidazole and 1-(*p*-Acetylphenyl)-2-methyl-4-nitroimidazole

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(*Received 11 March 1995; accepted 6 February 1996*)

Abstract

The title compounds, $C_{11}H_{11}N_3O_3$ and $C_{12}H_{11}N_3O_3$, are monomers. The angle between the planes of the phenyl and imidazole rings is 63.9 (6)° in the former compound and 51.8 (5)° in the latter. The nitro groups are twisted by 3.9 (5) and 5.1 (5)°, respectively, with respect to the imidazole rings.

Comment

As part of a study of radiosensitizing nitroimidazoles (Suwiński & Salwińska, 1982) and a continuation of