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Preparation and structural characterization of *N*-glycated amino acid and linear or cyclic dipeptides containing the 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose moiety

Mare Čudić [a], Biserka Kojić-Prodić [a,*], Vjekoslav Milinković [a], Jaroslav Horvat [a], Štefica Horvat [a], Mikael Elofsson [b], Jan Kihlberg [b]

[a] *Rudjer Bošković Institute, P.O. Box 1016, 10001 Zagreb, Croatia*

[b] *Organic Chemistry 2, Lund Institute of Technology, University of Lund, P.O. Box 124, S-22100 Lund, Sweden*

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Abstract

N-Glycated derivatives of glycine, glycylglycine, and 2,5-piperazinedione, containing the 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactos-6-yl moiety, were synthesized and studied by X-ray crystallography and NMR spectroscopy. The crystal structures of *N*-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactos-6-yl)glycine (**2**), its glycylglycine analogue (**3**), and 2,5-piperazinedione congener (**4**) were determined. The crystals of **2** are monoclinic; space group $P2_1$ with $a = 10.5098(5)$, $b = 5.7632(5)$, $c = 13.0938(7)$ Å, $\beta = 90.245(5)°$, $Z = 2$. The compounds **3** and **4** crystallized in the orthorhombic space group $P2_12_12_1$ with $a = 5.3429(9)$, $b = 15.1484(4)$, $c = 22.853(2)$ Å, $Z = 4$ (**3**) and $a = 28.69(6)$, $b = 15.478(3)$, $c = 15.504(2)$ Å, $Z = 4$ (**4**). In the solid state the α-D-galactopyranose moiety of **2** and **3** existed in the twisted $^{O}T_2$ conformation, whereas in **4** a transition state between $^{O}T_2$ and $^{O}S_2$ was recorded. ^{1}H NMR spectroscopy revealed that the conformation in solution for the galactopyranose moiety of compounds **2**–**4** closely resembled that found in the crystals. © 1996 Elsevier Science Ltd.

* Corresponding author.

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1. Introduction

In recent years various carbohydrate–amino acid conjugates linked through C–C, C–N, C–S, and C–O bonds have been synthesized and evaluated for their biological activity [1–4]. The rationale for this approach was that carbohydrates could partake in (a) organ or site delivery, by making use of their particular physicochemical properties, and (b) specific cell delivery, using the idea of carbohydrate receptors to route useful drugs to cell targets [5]. On the other hand, L-amino acids, as such, are actively transported into mammalian tissue and, hence, may serve as carriers.

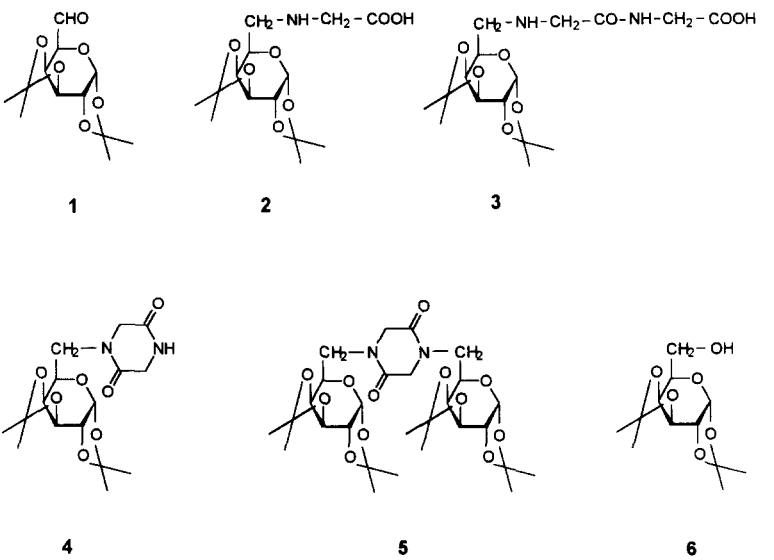
Much current attention is also focused on the synthesis, biological evaluation, and chemotherapeutic application of a variety of non-natural derivatives of amino sugars [6]. As a part of our programme devoted to modification of biologically active molecules by glycation, we report here the synthesis and structural analysis of a new class of pharmacologically interesting unnatural amino sugars that combine the structures of 6-amino-6-deoxy-D-galactose derivative and amino acid, dipeptide, and/or cyclic dipeptide in a single molecule sharing the same *N*-atom. The design and synthesis of these compounds originated from the finding that *N*-alkylation is an important modification of amino acids or peptides found to be accompanied by a series of structural, chemical, and biological effects [7,8] and that the carbohydrate units distally located on the cell surface, mainly D-galactose and sialic acid units, are involved in receptor function and density-dependent growth inhibition [9,10]. Modification of the D-galactose moiety is one approach that may lead to the development of anticancer chemotherapeutic agents since such carbohydrate analogues may become incorporated as components into the cell-surface glycoconjugates or interfere as antimetabolites with its cellular biosynthesis. We assume that the combination of structural features of protected D-galactose modified at C-6, being already part of the molecules with anticancer and antiviral activity [11,12], with linear or cyclic dipeptides, the latter also exhibiting interesting physiological and/or pharmacological activities in mammals [13], would result in glycoconjugates possessing interesting and beneficial biological activities.

Our interest in this work has been focused on the comparative structural analysis based on X-ray crystallographic studies and NMR spectroscopic data in order to obtain information about the conformation of the pyranose ring, and also the hydrogen-bond patterns, after *N*-glycation of amino acid, dipeptide, and cyclic dipeptide with rigid 6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactose moiety.

2. Results and discussion

Synthesis.—1,2:3,4-Di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**1**), the key intermediate in preparation of glycoconjugates **2** and **3**, was derived from 1,2:3,4-di-*O*-isopropylidene-α-D-galactose by using a chromium trioxide–dipyridine

complex as oxidant [14]. Reductive amination [15] of **1** by either glycine or glycylglycine in the presence of sodium cyanoborohydride afforded the *N*-alkylated derivatives **2** and **3** in 40% and 67% yield, respectively. The *N*-glycated-2,5-piperazinedione **4** was prepared by intramolecular cyclization involving N and C terminal groups of the linear dipeptide derivative **3**. Amide-bond formation was achieved by dissolving **3** in DMF at pH 7.5 employing benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and 1-hydroxybenzotriazole (HOBt) as cyclization reagents, and then allowing the solution to stand for 72 h. After purification by silica gel chromatography, the yield of **4** was 76%. Acyclic glycine derivative **2** was converted into *N,N'*-bis-glycated-2,5-piperazinedione **5** by following essentially identical reaction conditions. The cyclization yield was 58%. It is reasonable to assume that the first step in the formation of cyclic compound **5** involves activation of the C-terminal carboxyl group in **2** and self-condensation to give an *N,N'*-bis-glycated linear dipeptide derivative. In the second step, ring closure of the latter through in situ activation of the C-terminus furnished **5**. Compound **5** was also obtained by reductive amination of aldehyde **1** with *N*-glycated-2,5-piperazinedione **4** in the presence of sodium cyanoborohydride. However, this synthetic route is less efficient than the previous one giving **5** in 12% yield.



X-ray structure of **2**, **3**, *and* **4**.—The structures of **2**, **3**, and **4** with the atom numbering are shown in Figs. 1–3; the ORTEP [17] plots were drawn with thermal ellipsoids at the 30% probability level. Selected bond lengths and angles are listed in Table 1. In the crystalline state, molecules **2** and **3** are zwitterions (Figs. 1 and 2).

The endocyclic bonds C–O (C-5–O-5 and O-5–C-1, Table 1) in 1,2:3,4-di-*O*-isopropylidene-α-D-galactose rings are asymmetrical as was reported for α-D-pyranoses [18,19]. The mean value of valence angles C-5–O-5–C-1 [⟨113.2(4)°⟩ for **2**, **3**, and **4**] is in

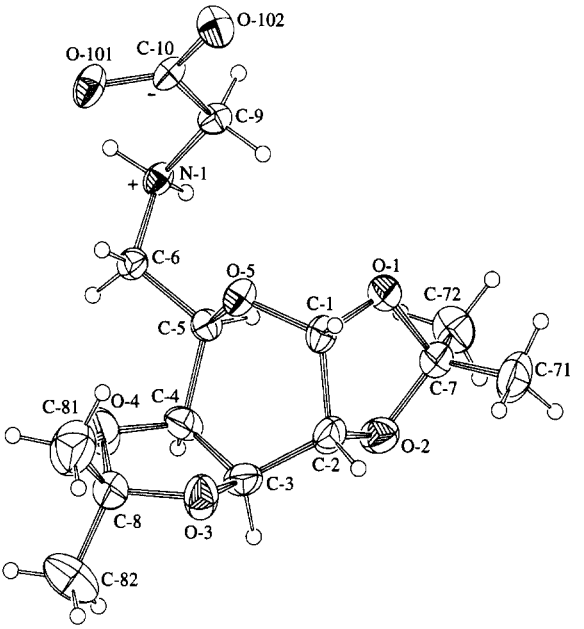


Fig. 1. ORTEP plot of **2**.

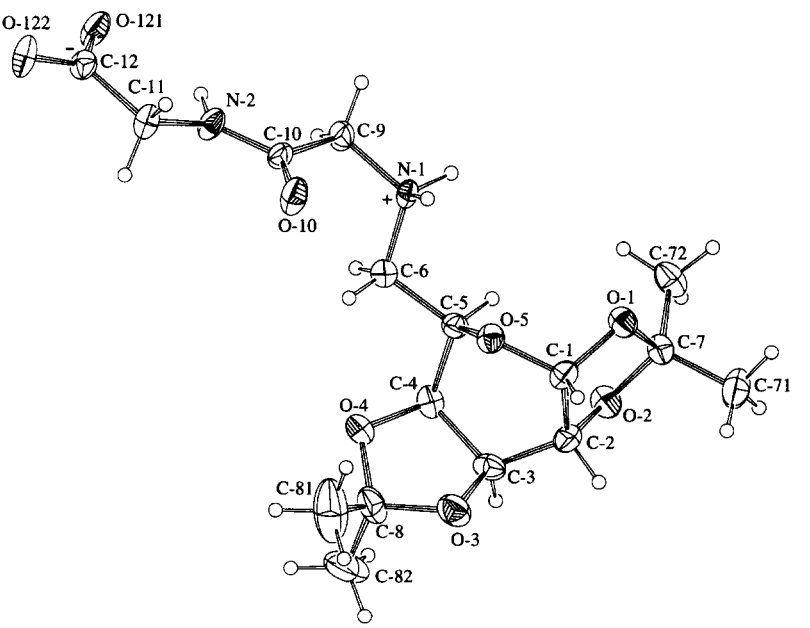


Fig. 2. ORTEP plot of **3**.

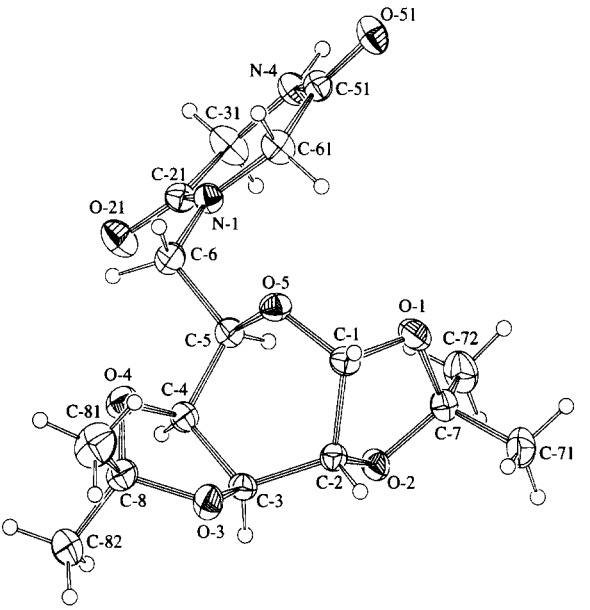


Fig. 3. ORTEP plot of **4**.

agreement with those observed for α-D-pyranoses in a chair $^4C_1$ conformation [18]. However, the angle O-5–C-1–O-1 is somewhat closed [⟨110.6(4)°⟩ for **2**, **3**, and **4**] due to the presence of isopropylidene rings which force the α-D-pyranose moiety to adopt a twisted conformation. The molecular geometry observed in these structures is in good agreement with the values observed in 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [21]; therefore it will not be discussed here.

The overall molecular conformation is described by selected torsion angles presented in Table 2. Ring conformational analysis of the α-D-galactopyranose ring and dioxolane rings were given in terms of Cremer–Pople parameters [20] and assigned according to the extended carbohydrate nomenclature [21] in Table 3; the illustration of $^{\circ}T_2$ detected in **2** is given in Fig. 4. The conformational analysis of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoses based on 31 data sets extracted from Cambridge Structural Database [22] by Köll et al. [21] revealed a heavily distorted conformation which was described as between the screw-boat $^{\circ}S_5$ and twist-boat $^{\circ}T_2$. The authors expanded the Cremer and Pople description [20] with the approach given by Boeyens [23] and developed a more detailed description including elements of definitions given by Schwarz [24] and Stoddart [25]. The dioxolane rings in most cases are in envelope conformation (Table 3) and in a single case (one of dioxolane rings of **2**) a transition form between envelope and twisted conformations was detected (Table 3). The heterocyclic 2,5-piperazinedione ring in **4** is close to planar; the mean torsion angle is 5.9(3)°.

The relative orientation of carbohydrate moiety towards the amino acid chain in **2** and **3** is defined by the torsion angle about the C-6–N-1 bond (Table 2): in **2** (+)synclinal conformation and in **3** (+)antiperiplanar conformation [26]. In the structure of **4** the

Table 1
Selected bond distances (Å) and angles (°) of **2**, **3**, and **4**

Bond distance	**2**	**3**	**4**
C-1–C-2	1.55(1)	1.535(7)	1.532(3)
C-2–C-3	1.54(1)	1.488(7)	1.525(3)
C-3–C-4	1.474(9)	1.549(8)	1.545(2)
C-4–C-5	1.51(1)	1.522(7)	1.506(3)
C-5–O-5	1.448(8)	1.440(6)	1.431(3)
O-5–C-1	1.410(7)	1.409(6)	1.405(2)
C-1–O-1	1.414(8)	1.406(5)	1.404(3)
O-1–C-7	1.449(9)	1.449(6)	1.439(3)
C-7–O-2	1.434(9)	1.421(5)	1.425(3)
O-2–C-2	1.40(1)	1.415(7)	1.429(3)
C-7–C-71	1.483(9)	1.500(8)	1.518(3)
C-7–C-72	1.50(1)	1.507(8)	1.510(4)
C-3–O-3	1.43(1)	1.417(7)	1.423(3)
O-3–C-8	1.427(8)	1.423(8)	1.431(3)
C-8–O-4	1.41(1)	1.426(7)	1.421(3)
O-4–C-4	1.470(9)	1.420(6)	1.423(3)
C-8–C-81	1.48(2)	1.49(1)	1.506(4)
C-8–C-82	1.47(1)	1.521(8)	1.515(4)
C-5–C-6	1.503(8)	1.515(7)	1.529(2)
C-6–N-1	1.477(8)	1.484(5)	1.467(3)
N-1–C-9	1.493(8)	1.488(6)	
C-9–C-10	1.51(1)	1.516(7)	
O-10–C-10		1.223(7)	
C-10–N-2		1.314(7)	
N-2–C-11		1.450(7)	
C-11–C-12		1.511(7)	
C-12–O-121 [a]	1.256(7)	1.257(7)	
C-12–O-122 [a]	1.248(8)	1.239(6)	
Bond angle	**2**	**3**	**4**
C-1–C-2–C-3	113.7(6)	113.9(4)	115.7(1)
C-2–C-3–C-4	115.1(6)	114.2(4)	114.4(2)
C-3–C-4–C-5	115.1(6)	111.3(4)	112.1(2)
C-4–C-5–O-5	109.0(5)	110.9(4)	109.6(2)
C-5–O-5–C-1	112.9(5)	112.9(4)	113.7(2)
O-5–C-1–C-2	113.5(5)	113.8(4)	114.8(2)
C-1–O-1–C-7	110.7(5)	109.4(3)	110.3(2)
O-1–C-7–O-2	102.3(5)	104.2(3)	104.6(2)
C-7–O-2–C-2	108.3(6)	106.6(4)	106.3(2)
O-2–C-2–C-1	104.1(6)	103.4(4)	103.3(2)
C-2–C-1–O-1	103.4(6)	104.4(4)	104.2(2)
O-1–C-7–C-71	108.6(7)	111.1(5)	110.3(2)
O-1–C-7–C-72	109.5(6)	107.2(4)	109.5(2)
O-2–C-7–C-71	112.8(7)	111.3(4)	111.0(2)
O-2–C-7–C-72	108.3(7)	109.7(5)	108.9(2)
C-71–C-7–C-72	114.6(7)	112.9(5)	112.3(2)
O-1–C-1–O-5	109.9(5)	111.6(4)	110.2(2)
O-2–C-2–C-3	107.1(7)	109.8(5)	107.9(2)

Table 1 (continued)

Bond angle	2	3	4
C-3–O-3–C-8	107.4(6)	105.5(5)	107.1(2)
O-3–C-8–O-4	104.9(7)	105.5(4)	104.4(2)
C-8–O-4–C-4	110.7(5)	109.6(4)	107.6(2)
O-4–C-4–C-3	103.0(6)	103.3(4)	104.5(2)
C-4–C-3–O-3	107.0(6)	104.5(5)	104.3(2)
O-3–C-8–C-81	107.1(8)	108.9(6)	109.0(2)
O-3–C-8–C-82	112.3(7)	110.3(5)	110.8(2)
O-4–C-8–C-81	109.5(9)	108.7(6)	109.1(2)
O-4–C-8–C-82	112.0(8)	109.9(6)	110.2(2)
C-81–C-8–C-82	110.8(8)	113.2(6)	112.9(3)
O-3–C-3–C-2	105.8(7)	109.8(5)	107.3(2)
O-4–C-4–C-5	107.8(6)	110.5(4)	108.9(2)
C-4–C-5–C-6	114.6(5)	110.1(4)	112.7(2)
O-5–C-5–C-6	106.6(5)	108.1(4)	107.8(2)
C-5–C-6–N-1	113.7(5)	111.1(4)	111.4(2)
C-6–N-1–C-9	115.8(5)	112.6(3)	
N-1–C-9–C-10	113.8(5)	111.8(4)	
C-9–C-10–O-101	118.4(6)		
C-9–C-10–O-102	115.5(5)		
O-101–C-10–O-102	126.1(7)		
C-9–C-10–O-10		122.9(5)	
C-9–C-10–N-2		112.9(5)	
O-10–C-10–N-2		124.2(5)	
C-10–N-2–C-11		124.0(5)	
N-2–C-11–C-12		110.5(5)	
C-11–C-12–O-121		117.4(4)	
C-11–C-12–O-122		117.4(5)	
O-121–C-12–O-122		125.2(5)	

[a] In **2**, carboxylic group atom numbering: C-10, O-101, and O-102.

2,5-piperazinedione ring is almost perpendicular to the C-5–C-6 bond; the conformation about the C-6–N-1 bond is (+)anticlinal.

Crystal packing and hydrogen bonds.—The crystal packing of **2**, **3**, and **4** is given in Figs. 5–7 and in Table 4. Deprotonated carboxylic groups of **2** and **3** are involved in intra- and inter-molecular hydrogen bonds with the amino groups. In **2** one of the protons of the amino group (H-11) is involved in a bifurcated hydrogen bond between intra- and inter-molecular O-101 of the carboxylic group; the proton H-12 participates in intermolecular hydrogen bonds with O-102. However, in **3** there is no bifurcated hydrogen bond. The amide group N-2 adjacent to the carboxylic group forms an intramolecular hydrogen bond whereas the protonated amino group (N-1) acts as a proton donor to two different molecules involving O-121 and O-122; the two-dimensional network is completed. The crystal packing of **4** contains an infinite chain along **a** formed by N–H · · · O hydrogen bonds.

NMR studies of **2**, **3**, **4**, *and* **5**.—To allow a comparison with the structures of **2**–**4** in the crystals, the conformations in solution were investigated using ^{1}H NMR spec-

Table 2
Selected torsion angles (°) of **2**, **3**, and **4**

Torsion angle	**2**	**3**	**4**
C-1–C-2–C-3–C-4	39(1)	46.8(7)	34.7(3)
C-2–C-3–C-4–C-5	−14(1)	−19.1(7)	−0.9(3)
C-3–C-4–C-5–O-5	−37.8(8)	−36.0(5)	−49.2(2)
C-4–C-5–O-5–C-1	69.9(6)	68.9(4)	70.0(2)
C-5–O-5–C-1–C-2	−43.1(7)	−39.6(5)	−33.7(2)
O-5–C-1–C-2–C-3	−11.1(9)	−17.7(7)	−18.5(3)
C-1–O-1–C-7–O-2	24.9(7)	20.1(5)	18.1(2)
O-1–C-7–O-2–C-2	−34.4(6)	−33.9(5)	−32.2(2)
C-7–O-2–C-2–C-1	30.3(6)	33.7(5)	33.2(2)
O-2–C-2–C-1–O-1	−13.9(6)	−20.6(5)	−21.5(2)
C-2–C-1–O-1–C-7	−7.1(7)	0.3(5)	2.2(2)
C-1–O-1–C-7–C-71	−94.7(7)	−99.9(5)	−101.3(2)
C-1–O-1–C-7–C-72	139.5(6)	136.3(4)	134.6(2)
C-2–O-2–C-7–C-71	82.1(8)	85.9(5)	86.7(2)
C-2–O-2–C-7–C-72	−149.9(6)	−148.4(4)	−149.2(2)
C-7–O-1–C-1–O-5	−128.6(6)	−123.1(4)	−121.5(2)
C-7–O-2–C-2–C-3	151.1(5)	155.6(4)	156.1(1)
O-1–C-1–O-5–C-5	72.1(7)	78.3(5)	83.6(2)
O-1–C-1–C-2–C-3	−130.1(7)	−139.7(5)	−139.1(2)
O-2–C-2–C-3–C-4	−74.9(9)	−68.6(6)	−80.3(2)
O-2–C-2–C-3–O-3	167.2(6)	174.5(3)	164.5(1)
O-2–C-2–C-1–O-5	105.1(6)	101.4(4)	99.1(2)
C-3–O-3–C-8–O-4	−26.3(9)	−34.3(5)	−34.6(2)
O-3–C-8–O-4–C-4	18(1)	22.8(6)	33.4(2)
C-8–O-4–C-4–C-3	−2(1)	−3.1(5)	−19.4(2)
O-4–C-4–C-3–O-3	−14.0(9)	−17.7(5)	−1.8(2)
C-4–C-3–O-3–C-8	25.4(9)	31.8(5)	22.1(2)
C-3–O-3–C-8–C-81	−142.6(8)	−150.8(6)	−151.1(2)
C-3–O-3–C-8–C-82	95.6(8)	84.4(5)	84.0(2)
C-4–O-4–C-8–C-81	132.1(9)	139.5(6)	149.9(2)
C-4–O-4–C-8–C-82	−104.6(9)	−96.2(6)	−85.6(2)
C-8–O-3–C-3–C-2	148.6(6)	154.6(4)	143.8(2)
C-8–O-4–C-4–C-5	−124.3(7)	−122.2(5)	−139.3(2)
O-3–C-3–C-2–C-1	−78.4(8)	−70.1(6)	−80.5(2)
O-3–C-3–C-4–C-5	103.1(7)	100.9(5)	116.0(2)
O-4–C-4–C-5–O-5	76.5(6)	78.2(5)	65.9(2)
O-4–C-4–C-3–C-2	−131.2(8)	−137.6(5)	−118.7(2)
C-3–C-4–C-5–C-6	−157.1(7)	−155.6(5)	−169.3(2)
C-1–O-5–C-5–C-6	−165.9(5)	−170.3(3)	−167.0(2)
O-4–C-4–C-5–C-6	−42.8(8)	−41.5(6)	−54.2(2)
C-4–C-5–C-6–N-1	−153.5(6)	−174.0(5)	−147.0(2)
O-5–C-5–C-6–N-1	85.8(6)	64.6(6)	91.9(2)

Table 2 (continued)

Torsion angle	2	3	4
C-5–C-6–N-1–C-21			109.0(2)
C-5–C-6–N-1–C-9	−62.7(7)	169.4(5)	
C-6–N-1–C-9–C-10	−71.5(6)	69.6(6)	
N-1–C-9–C-10–O-101	−3.7(8)		
N-1–C-9–C-10–O-102	176.5(5)		
N-1–C-9–C-10–O-10		22.1(7)	
N-1–C-9–C-10–N-2		−158.7(4)	
C-9–C-10–N-2–C-11		−168.4(4)	
O-10–C-10–N-2–C-11		10.8(8)	
C-10–N-2–C-11–C-12		166.3(5)	
N-2–C-11–C-12–O-121		−0.5(6)	
N-2–C-11–C-12–O-122		−179.1(4)	

troscopy. Compounds **2** and **3** were studied both in Me_2SO-d_6 and in aq (D_2O) solution at pH ~ 5.5, whereas the solubility of **4** and **5** allowed studies only in Me_2SO-d_6.

The chemical shifts of the protons H-1–H-5 on the galactopyranose ring display very little variation (< 0.1 ppm differences) between compounds **2–5**, as shown in Table 5. One exception is H-5 in the glycated glycylglycine **3** which in Me_2SO-d_6 displays a 0.2 ppm upfield shift, as compared to **3** in D_2O or to H-5 in compounds **2**, **4**, and **5**. Another exception are the exocyclic protons H-6,6′ in **2** and **3** which in Me_2SO-d_6 show significant upfield shifts as compared to in D_2O. Formation of an intramolecular hydrogen bond, in Me_2SO-d_6 but not in D_2O, between the N- and C-termini of the zwitterionic **2** and **3** provides a possible explanation for these upfield shifts. Support for this explanation is provided by the observation of such a hydrogen bond in the crystal of the glycated glycine **2**. However, further NMR investigations were initiated to clear up this assumption.

Table 3
Ring conformational analysis in the X-ray structures of **2**, **3**, and **4**

	Cremer–Pople parameters [20]			Conformation		
Compounds Atom sequence	2	3	4	2	3	4
α-D-galactopyranose ring C-1–C-2–C-3–C-4–C-5–O-5	Q = 0.637 Å Θ = 78.8° Φ = 329.0°	Q = 0.660 Å Θ = 83.2° Φ = 330.2°	Q = 0.624 Å Θ = 77.2° Φ = 317.9°	$^{O}T_{2}$	$^{O}T_{2}$	$^{O}T_{2}$ / $^{O}S_{2}$
Dioxolane ring C-1–O-1–C-7–O-2–C-2	Q = 0.308 Å Φ = 298.6°	Q = 0.317 Å Φ = 286.2°	Q = 0.312 Å Φ = 283.3°	E/T	E	E
Dioxolane ring C-3–O-3–C-8–O-4–C-4	Q = 0.240 Å Φ = 174.2°	Q = 0.311 Å Φ = 176.5°	Q = 0.314 Å Φ = 146.8°	E	E	E

Table 4
Hydrogen bond geometry of **2**, **3**, and **4**

Compound		$D \cdots A$ (Å)	D–H (Å)	H $\cdots$ A (Å)	D–H $\cdots$ A (°)	Symmetry operation on A
2	N-1–H-11 $\cdots$ O-101	2.728(8)	1.009 [a]	2.510(8)	91(6)	x, y, z
	N-1–H-11 $\cdots$ O-101	2.776(6)	1.009	1.814(6)	158(6)	$-x+2, 1/2+y, -z+1$
	N-1–H-12 $\cdots$ O-102	2.677(8)	1.009	1.677(8)	170(6)	$x, y+1, z$
3	N-1–H-11 $\cdots$ O-121	2.663(5)	1.009	1.657(5)	174(3)	$-x, 1/2+y, 1/2-z$
	N-1–H-12 $\cdots$ O-122	2.732(6)	1.009	1.794(6)	153(3)	$-x+1, 1/2+y-1, 1/2-z$
	N-2–H-21 $\cdots$ O-121	2.610(6)	1.009	2.11(5)	108(3)	x, y, z
4	N-4–H-49 $\cdots$ O-51	2.691(3)	1.009	1.73(4)	158(3)	$1/2+x-1, 1/2-y, -z$

[a] N–H distances are normalized to the value of 1.009 Å (neutron data).

Table 5
^{1}H NMR chemical shifts for compounds **2**, **3**, **4**, and **5** [a]

Residue	Protons	δ (ppm)					
		2 [b]	**2** [c]	**3** [b]	**3** [c]	**4** [b]	**5** [b]
Gal	H-1	5.59	5.60	5.53	5.59	5.53	5.53
	H-2	4.48	4.46	4.42	4.45	4.43	4.44
	H-3	4.71	4.70	4.68	4.70	4.69	4.70
	H-4	4.30	4.35	4.32	4.34	4.29	4.30
	H-5	4.02	4.05	3.86	4.03	4.08	4.07
	H-6/H-6′	3.08/2.97	3.25	2.76	3.24	3.53/3.44	3.60/3.43
Gly	NH	– [d]		– [d]			
	α/α′	3.25	3.51	3.26	3.86/3.80	4.02	4.10
Gly	NH			8.20		8.25	
	α/α′			3.86	3.86/3.80	3.88	4.10
Isopropylidene	CH_3	1.59, 1.45, 1.38	1.46, 1.37, 1.28	1.55, 1.43, 1.38	1.44, 1.36, 1.27	1.49, 1.47, 1.39, 1.36	1.50, 1.47, 1.39, 1.36

[a] Obtained at 500.14 MHz and 294 K.
[b] In Me_2SO-d_6 with Me_2SO-d_5 (δ_H 2.60 ppm) as internal standard.
[c] In D_2O with HOD (δ_H 4.98 ppm) as internal standard at pH 5.7 for **2** and pH 5.4 for **3**, respectively.
[d] Not observed.

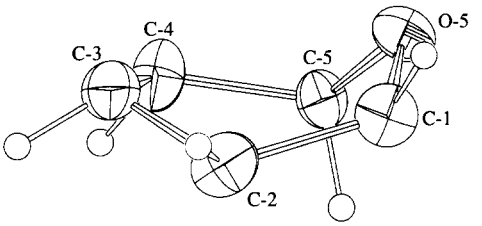


Fig. 4. $^{o}T_{2}$ conformation of α-D-galactopyranose ring in **2**.

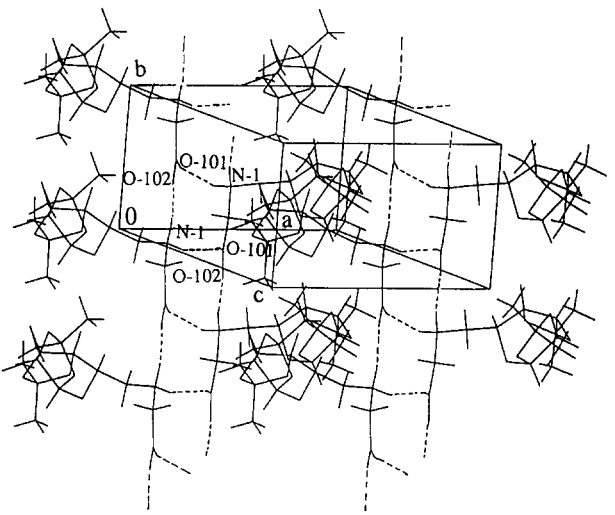


Fig. 5. Crystal packing of **2**.

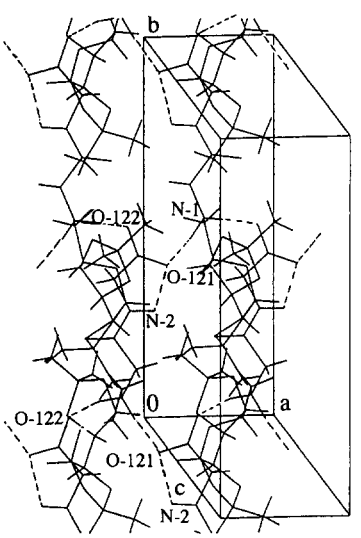


Fig. 6. Crystal packing of **3**.

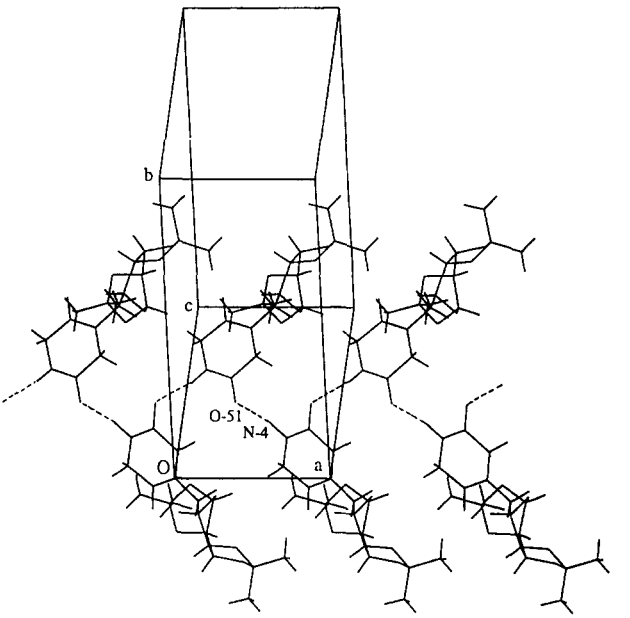


Fig. 7. Crystal packing of **4**.

The $^{3}J_{H,H}$ coupling constants between the protons on the galactopyranose ring of **2–5** show almost no variation (Table 6) and agree very well with those calculated for the minimum energy conformation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**) [16]. Furthermore the calculated values for the torsional angles between the ring protons in **6** agree well with those found in the crystals of **2–4** (Table 7) revealing that the solution conformation of the pyranose ring for **2–4** is closely related to that in the crystal. This is not unexpected since the two isopropylidene rings severely restrict the

Table 6
Observed and calculated [16] coupling constants (*J*, Hz) for the pyranose moiety in compounds **2**, **3**, **4**, **5** [a], and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**) [16]

Protons	Observed						Calculated [16]
	2 [b]	**2** [c]	**3** [b]	**3** [c]	**4** [b]	**5** [b]	**6**
1-2	5.0	5.0	5.0	5.0	5.0	5.0	4.77
2-3	2.4	2.5	2.3	2.5	2.4	2.4	2.62
3-4	7.9	7.9	7.9	7.9	7.9	7.9	7.87
4-5	1.9	2.0	1.9	1.9	1.8	1.7	1.85
5-6*S*							4.65
	3.2/9.0	4.2/7.1	5.7/7.3	4.2/8.9	4.4/8.7		
5-6*R*							8.10

[a] Obtained at 500.14 MHz and 294 K.
[b] In Me_2SO-d_6 with Me_2SO-d_5 (δ_H 2.60 ppm) as internal standard.
[c] In D_2O with HOD (δ_H 4.98 ppm) as internal standard at pH 5.7 for **2** and pH 5.4 for **3**, respectively.

Table 7
The torsional angles (°) between the protons of the galactopyranose ring observed in the crystals of **2–4** and calculated values for the minimum energy conformation of **6** from ref. [16]

Torsional angle	Observed			Calculated [16]
	2	**3**	**4**	**6**
H-1–C-1–C-2–H-2	−12(1)	−19.7(7)	−24(2)	−22
H-2–C-2–C-3–H-3	−72(1)	−66.5(9)	−84(2)	−69
H-3–C-3–C-4–H-4	−13(1)	−18.8(8)	−1(3)	−8
H-4–C-4–C-5–H-5	−44(1)	−38.7(7)	−52(2)	−49
H-5–C-5–C-6–H-61	89(1)	66.7(7)	91(3)	64 (5-6*S*)
H-5–C-5–C-6–H-62	−153(1)	−175.1(7)	−144(2)	−172 (5-6*R*)

conformational freedom of the pyranose ring. Studies of derivatives of **6** selectively deuterated at C-6 revealed the synclinal/antiperiplanar conformation to be preferred about the C-5–C-6 bond for **6** in chloroform solution [16]. Assignment of the H-6*S* and H-6*R* protons in **2–5** would have required selective deuteration which was not performed. However, the observed coupling constants between H-5 and H-6,6′ in **2–5** agree well with those for **6** suggesting that the synclinal/antiperiplanar conformation could well be preferred also for solutions of **2–5**. This is further supported by the fact that the synclinal/antiperiplanar conformation about the C-5–C-6 bond is found in the crystals of **2–4** (cf. Figs. 1–3 and Table 2).

3. Experimental

General methods.—Melting points were determined in capillaries and are uncorrected. Optical rotations were measured using an Optical Activity LTD automatic AA-10 Polarimeter. Column chromatography was performed on Silica Gel (E. Merck, 0.040–0.063 mm) and TLC on Silica Gel 60 with detection with ninhydrin, the chlorine–iodine reagent, or charring with H_2SO_4. The solvents used were: (A) MeOH–EtOAc–AcOH (50:20:0.5); (B) EtOAc–MeOH (6:1); (C) EtOAc–toluene (10:1). The structures of the compounds were confirmed by microanalysis (C, H, N) and by NMR spectroscopy using a Varian Gemini 300 spectrometer operating at 75.5 MHz (^{13}C) and 300.1 MHz (^{1}H).

N-*(6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactos-6-yl)glycine* (**2**).—To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**1**) [14] (387 mg, 1.5 mmol) in MeOH–H_2O (30 mL, 1:1) were added glycine (75 mg, 1 mmol) and $NaBH_3CN$ (66 mg, 1 mmol), and the mixture was stirred for 5 h at 343 K. After cooling (ice-bath), the pH of the mixture was adjusted to 5.5 with 2 N HCl, and the stirring was continued for another 30 min until the unreacted $NaBH_3CN$ was destroyed. The mixture was evaporated, and the residue was chromatographed on a column of silica gel with the solvent (A) to give the compound **2** as acetate salt (150 mg, 40%); mp 478–483 K; $[\alpha]_D^{25}$ −38.0° (*c* 1.0, H_2O). Anal. Calcd for $C_{16}H_{27}NO_9$: C, 50.92; H, 7.21; N, 3.71. Found: C, 50.72; H, 7.35; N, 4.00.

N-*(6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactos-6-yl)glycylglycine* (**3**).—To a solution of **1** (516 mg, 2 mmol) in MeOH–H_2O (30 mL, 1:1) were added glycylglycine

(132 mg, 1 mmol) and $NaBH_3CN$ (66 mg, 1 mmol), and the mixture was stirred for 5 h at 343 K. After cooling (ice-bath), the pH of the mixture was adjusted to 5.0 with 2 N HCl, and the stirring was continued for another 30 min until the unreacted $NaBH_3CN$ was destroyed. The mixture was evaporated, and the residue was chromatographed on a column of silica gel with the solvent (A) to give the compound **3** (250 mg, 67%); mp

Table 8
Crystal data and summary of experimental details

	2	**3**	**4**
(a) Crystal data			
Molecular formula	$C_{14}H_{23}NO_7$	$C_{16}H_{26}N_2O_8$	$C_{16}H_{24}N_2O_7$
M_r	317.34	374.9	356.42
Crystal size [mm]	0.14×0.08×0.28	0.07×0.07×0.25	0.4×0.18×0.15
a [Å]	10.5098(5)	5.3429(5)	7.2869(6)
b [Å]	5.7632(5)	15.1484(4)	15.478(3)
c [Å]	13.0938(7)	22.853(2)	15.504(2)
α [°]	90	90	90
β [°]	90.245(4)	90	90
γ [°]	90	90	90
V [Å^3]	793.09(9)	1849.6(2)	1748.6(4)
Crystal system	monoclinic	orthorhombic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
D_x [g cm^{-3}]	1.3288(2)	1.3444(1)	1.3536(3)
Z	2	4	4
μ (Cu $K\alpha$) [cm^{-1}]	8.6	8.7	8.6
$F(000)$	340	800	760
(b) Data collection			
T [K]	297(3)	297(3)	297(3)
No. of reflections used for cell determination	25	22	15
θ range [°] used for cell determination	9.4; 45.6	11.7; 43.7	9.5; 10.7
θ range [°] for intensity measurement	2.37; 74.33	2.15; 74.33	2.1; 74.33
hkl limits	−13, 13; −7, 0; −16, 0	0, 6; −18, 0; −28, 0	0, 9; −19, 0; 0, 19
$\omega/2\theta$ scan	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
No. of measured reflections	1913	2300	2122
(c) Refinement			
No. of symm. independent refl. $I > 3\sigma(I)$	1495	2213	2053
No. of variables	217	256	267
Goodness of fit	1.217	0.917	0.689
Flack parameter x	0.03(70)	0.7(6)	0.27(25)
R [$F_o > 4\sigma(F_o)$]	$R_1 = 0.066$ (1080)	$R_1 = 0.048$ (1204)	$R_1 = 0.0375$ (1833)
R (all data)	$R_1 = 0.1157$; $wR_2 = 0.2149$	$R_1 = 0.1733$; $wR_2 = 0.1725$	$R_1 = 0.0459$; $wR_2 = 0.1197$
Final shift/error $(\Delta/\sigma)_{max}$	0.08	0.06	0.04
Residual electron density $(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ [e Å^{-3}]	0.23; −0.29	0.269; −0.321	0.165; −0.223

487–489 K (decomp); $[\alpha]_D^{25}$ −63° (*c* 1.0, H_2O). Anal. Calcd for $C_{16}H_{26}N_2O_8$: C, 51.31; H, 7.01; N, 7.48. Found: C, 51.24; H, 6.86; N, 7.42.

*1-(6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactos-6-yl)-2,5-piperazinedione* (**4**). —To a solution of *N*-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactos-6-yl)glycylglycine (**3**) (37 mg, 0.1 mmol) in dry DMF (10 mL) were added under stirring BOP (49 mg, 0.11 mmol), HOBt (12 mg, 0.1 mmol), and NMM until the pH was 7.5. The mixture was stirred for 72 h. The solvent was evaporated and the residue was chromatographed on a column of silica gel with the solvent (B) to give the compound (**4**) (27 mg, 76%); mp 515–517 K; $[\alpha]_D^{25}$ +4° (*c* 1.0, MeOH). Anal. Calcd for $C_{16}H_{24}N_2O_7$: C, 53.92; H, 6.80; N, 7.86. Found: C, 53.76; H, 7.00; N, 7.89. MS(M^+) 356; Calcd 356.

*1,4-bis-(6-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-*D*-galactos-6-yl)-2,5-piperazinedione* (**5**).—To a solution of *N*-(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactos-6-yl)glycine (**2**) acetate salt (75 mg, 0.2 mmol) in dry DMF (10 mL) was added under stirring BOP (150 mg, 0.3 mmol), HOBt (24 mg, 0.2 mmol), and NMM until the pH was 7.5. The mixture was stirred for 72 h. The solvent was evaporated and the residue was chromatographed on a column of silica gel with the solvent (C) to give the very hygroscopic compound **5** (35 mg, 41%); mp 393 K (decomp), $[\alpha]_D^{25}$ +1° (*c* 0.95, MeOH). Anal. Calcd for $C_{28}H_{42}N_2O_{12} \cdot 6H_2O$: C, 47.58; H, 7.72; N, 3.95. Found: C, 47.33; H, 6.60; N, 3.75. FABMS $[M + H]^+$ 599; Calcd 598.

Table 9
Final coordinates and equivalent isotropic thermal parameters of the non-hydrogen atoms for **2**

Atom	*x*	*y*	*z*	U_{eq} (Å) [a]
O-1	0.8023(5)	0.005(1)	0.0690(3)	0.054(2)
O-2	0.6680(5)	0.308(1)	0.0654(4)	0.061(2)
O-3	0.4425(5)	0.053(1)	0.2352(3)	0.067(2)
O-4	0.5560(5)	0.131(2)	0.3772(3)	0.093(3)
O-5	0.7301(4)	−0.09769(8)	0.2294(3)	0.047(2)
O-101	0.9447(5)	−0.4013(9)	0.4337(3)	0.056(2)
O-102	1.0219(5)	−0.5426(9)	0.2879(4)	0.058(2)
N-1	0.9576(5)	0.049(1)	0.3702(3)	0.039(2)
C-1	0.6957(6)	−0.069(2)	0.1259(4)	0.048(2)
C-2	0.5967(7)	0.127(2)	0.1076(5)	0.057(3)
C-3	0.5366(7)	0.220(2)	0.2063(5)	0.058(2)
C-4	0.6249(6)	0.245(2)	0.2934(5)	0.057(3)
C-5	0.7510(6)	0.122(1)	0.2812(4)	0.040(2)
C-6	0.8179(6)	0.066(1)	0.3798(4)	0.041(2)
C-7	0.7713(7)	0.208(2)	0.0090(4)	0.056(3)
C-8	0.4352(7)	0.055(2)	0.3440(5)	0.061(3)
C-9	1.0053(6)	−0.139(1)	0.3019(5)	0.038(2)
C-10	0.9889(6)	−0.381(1)	0.3452(4)	0.043(2)
C-71	0.733(1)	0.133(2)	−0.0950(4)	0.089(4)
C-72	0.8810(9)	0.375(2)	0.0121(7)	0.074(3)
C-81	0.415(1)	−0.188(3)	0.3771(9)	0.107(5)
C-82	0.3328(7)	0.205(2)	0.3813(9)	0.099(5)

[a] $U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* \cdot a_j^* \, \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

X-ray structure determination of **2**, **3**, *and* **4**.—Crystals suitable for X-ray analysis were grown from water (**2** and **3**) and ethanol (**4**) at about 298 K for 4 days. The crystal data and a summary of the experimental details are listed in Table 8. The X-ray intensities were collected on an Enraf–Nonius CAD4 diffractometer with Cu $K\alpha$ graphite-monochromatized radiation. There were no significant variations in intensity for standard reflections. The data were corrected for Lorentz and polarization effects using the programme HELENA [27]. The structures were solved by the SHELX-86 [28] programme and refined on F^2 using the SHELX-93 [29] programme. The H-atom coordinates in **4** were located from the subsequent difference Fourier synthesis. The same procedure was used to locate the H atoms attached to the pyranose ring and amino groups in **2** and **3** whereas the others were calculated on stereochemical grounds and refined riding on their respective C atoms. Atomic scattering factors were those included in SHELX-93 [29]. Details of the refinement procedure are given in Table 8. In the structure determination the D-enantiomers were selected according to the assignment (*R*) at the C-5 atoms; The Flack parameter in these structures cannot define the enantiomer unambiguously (Table 8). The molecular geometries were calculated by the programme EUCLID [30]. Drawings were prepared by the programme PLUTON [30] incorporated

Table 10
Final coordinates and equivalent isotropic thermal parameters of the non-hydrogen atoms for **3**

Atom	*x*	*y*	*z*	U_{eq} (Å) [a]
O-1	0.5483(8)	0.3530(2)	0.3635(1)	0.044(1)
O-2	0.2898(8)	0.3293(2)	0.4405(1)	0.047(1)
O-3	0.5816(9)	0.5026(3)	0.5253(1)	0.057(2)
O-4	0.3170(9)	0.6060(3)	0.4889(1)	0.052(1)
O-5	0.5611(7)	0.5011(2)	0.3907(1)	0.040(1)
O-10	0.5709(8)	0.7608(3)	0.3061(2)	0.055(2)
O-121	−0.0242(8)	0.9718(2)	0.2369(1)	0.054(1)
O-122	0.2722(8)	1.0724(2)	0.2492(1)	0.055(1)
N-1	0.2860(9)	0.6063(2)	0.3066(1)	0.033(1)
N-2	0.237(1)	0.8417(3)	0.2801(2)	0.043(2)
C-1	0.621(1)	0.4138(3)	0.4068(2)	0.041(2)
C-2	0.487(1)	0.3821(3)	0.4624(2)	0.046(2)
C-3	0.384(1)	0.4548(4)	0.4989(2)	0.045(2)
C-4	0.236(1)	0.5251(3)	0.4639(2)	0.040(2)
C-5	0.301(1)	0.5218(3)	0.3991(2)	0.035(2)
C-6	0.250(1)	0.6105(3)	0.3709(2)	0.045(2)
C-7	0.381(1)	0.2881(3)	0.3889(2)	0.042(2)
C-8	0.484(1)	0.5885(4)	0.5361(2)	0.059(2)
C-9	0.193(1)	0.6867(3)	0.2761(2)	0.042(2)
C-10	0.354(1)	0.7666(3)	0.2893(2)	0.037(2)
C-11	0.360(1)	0.9270(3)	0.2791(2)	0.046(2)
C-12	0.189(1)	0.9963(3)	0.2534(2)	0.038(2)
C-71	0.518(2)	0.2042(4)	0.4028(3)	0.067(3)
C-72	0.169(1)	0.2747(4)	0.3463(2)	0.056(2)
C-81	0.694(2)	0.6536(5)	0.5338(5)	0.118(4)
C-82	0.342(2)	0.5901(6)	0.5938(2)	0.094(3)

[a] $U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* \cdot a_j^* \, \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

Table 11
Final coordinates and equivalent isotropic thermal parameters of non-hydrogen atoms for **4**

Atom	*x*	*y*	*z*	U_{eq} (Å) [a]
O-1	0.6715(3)	0.3298(1)	0.3298(1)	0.0512(5)
O-2	0.5845(2)	0.4473(1)	0.4067(1)	0.0396(5)
O-3	0.9971(3)	0.5688(1)	0.3667(1)	0.0451(5)
O-4	0.9241(3)	0.5987(1)	0.2286(1)	0.0476(5)
O-5	0.8169(2)	0.4215(1)	0.2348(1)	0.0391(5)
O-21	0.3630(3)	0.5741(1)	0.0543(1)	0.0564(7)
O-51	0.4110(3)	0.2300(1)	0.0408(1)	0.0482(5)
N-1	0.5252(3)	0.4535(1)	0.0856(1)	0.0361(5)
N-4	0.2406(3)	0.34400(1)	0.0258(1)	0.0406(5)
C-1	0.8140(3)	0.3901(1)	0.3198(1)	0.0365(6)
C-2	0.7755(3)	0.4584(1)	0.3890(1)	0.0335(5)
C-3	0.8054(3)	0.5519(1)	0.3614(1)	0.0336(5)
C-4	0.7563(3)	0.5707(1)	0.2663(1)	0.0363(6)
C-5	0.6911(3)	0.4910(1)	0.2199(1)	0.0348(6)
C-6	0.6762(4)	0.5043(2)	0.1224(1)	0.0422(7)
C-7	0.5473(4)	0.3575(2)	0.3964(1)	0.0416(6)
C-8	1.0421(3)	0.6251(2)	0.2966(1)	0.0429(7)
C-21	0.3747(3)	0.4959(1)	0.0577(1)	0.0381(6)
C-31	0.2109(4)	0.4422(2)	0.0326(2)	0.0530(8)
C-51	0.3915(3)	0.3092(2)	0.0483(1)	0.0374(6)
C-61	0.5471(3)	0.3607(2)	0.0860(1)	0.0431(7)
C-71	0.5846(5)	0.3084(2)	0.4793(1)	0.0599(9)
C-72	0.3520(4)	0.3466(2)	0.3657(2)	0.061(1)
C-81	1.2383(4)	0.6096(3)	0.2703(2)	0.072(1)
C-82	1.0045(5)	0.7184(2)	0.3203(1)	0.063(1)

[a] $U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* \cdot a_j^* \, \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

in EUCLID and ORTEP [17]. The final atomic coordinates and equivalent isotropic thermal parameters are listed in Tables 9–11. Calculations were performed on Silicon Graphics, INDIGO-2 computer of the X-ray laboratory, Rudjer Bošković Institute, Zagreb, Croatia.

NMR Spectroscopy.—NMR samples of compounds **2**, **3**, **4**, and **5** were prepared by dissolving 5–6 mg of each compound in 0.7 mL Me_2SO-d_6. Samples of **2** and **3** were also prepared in D_2O at approximately the same concentrations. The pH for **2** in D_2O was adjusted to 5.7 with a solution of 0.04% NaOD in D_2O, whereas the pH for **3** was 5.4. One- and two-dimensional (COSY) spectra were recorded at 294 K on a Bruker AM 500 spectrometer operating at 500.14 MHz. The solvent signal was used as internal standard (residual Me_2SO-d_5 2.60 ppm; HOD 4.98 ppm). First order chemical shifts and coupling constants were obtained from one-dimensional spectra, and assignments of proton resonances were based on COSY experiments.

4. Supplementary material

The observed and calculated structure factors, H-atom coordinates, and anisotropic thermal parameters have been deposited with the Cambridge Crystallographic Data

Centre. The data may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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