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ON THE UNEXPECTED FORMATION OF A NEW DIOXOPIPERAZINE CONTAINING CARBOHYDRATE SIDE-CHAINS: AN X-RAY STUDY

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ABSTRACT

(3*R*,6*R*)-Bis[(1*R*,2*S*,3*R*)-tetrahydroxybutyl)]-2,5-dioxopiperazine ($C_{12}H_{22}N_2O_{11}$), obtained by cyclization of methyl 2-amino-2-deoxy-D-gluconate, gave orthorhombic crystals with space group $C222_1$, $a = 6.542(1)$, $b = 7.318(1)$, $c = 30.571(3)$ Å, $V = 1463.7(6)$ Å^3, $Z = 4$, and $D_x = 1.61$ g.cm^{-3}. The sugar side-chains were linked pseudo equatorially to the dioxopiperazine ring of C_2 molecular symmetry and were close packed (packing coefficient, 0.81) *via* four-fold rings of OH···O hydrogen bonds. Each sugar side-chain participates in eight hydrogen bonds with four neighbouring molecules, which produce closely packed 2-dimensional layers, possibly even in solution.

INTRODUCTION

In an attempt to prepare peptides containing a 2-amino-2-deoxyaldonic acid residue, the hydrochloride of methyl 2-amino-2-deoxy-D-gluconate was reacted with the mixed anhydride or other activated derivatives[1] of N^{α}-Boc-L-proline in the presence of 1 equiv. of triethylamine or *N*-methylmorpholine. Instead of the expected "glycopeptide", a poorly soluble, crystalline substance was isolated in excellent yield and shown to be (3*R*,6*R*)-bis[(1*R*,2*S*,3*R*)-tetrahydroxybutyl)]-2,5-dioxopiperazine ($C_{12}H_{22}N_2O_{11}$) (**1**).

Dioxopiperazines are the simplest constrained models used for conformational studies of peptides[2], and the derivative **1** also has the broad-scale hydrogen-bonding ability of the sugar moieties which makes it a suitable model for studying backbone–side-chain interactions which may be effective in glycopeptides.

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We now report on the solid-state conformation of **1** together with semi-empirical quantum chemical calculations and compare the structure with that[3] of *cyclo*(L-Ser-L-Ser) (**2**).

EXPERIMENTAL

T.l.c. was performed on Kieselgel 60 (5553, Merck). The c.d. spectrum was recorded on a Jobin–Yvon Dichrograph Mark III operated by a Kontron PSI 80 D computer. I.r. spectra were recorded in KBr with a Zeiss Specord IR 75 instrument.

(3R,6R)-Bis[(1R,2S,3R)tetrahydroxybutyl]-2,5-dioxopiperazine. — A solution of methyl 2-amino-2-deoxy-D-gluconate hydrochloride (6.54 mmol) in *N,N*-dimethylformamide (5 mL) was stirred with Et_3N (1.3 mL) for 15 min at room temperature and then concentrated, and the residue was crystallized from water to give **1** (0.91 g, 79.0%), m.p. 230° (dec.), $[\alpha]_D$ +39° (*c* 0.1 water), R_F 0.3 (BuOH–AcOH–H_2O, 2:1:1); ν_{max} 3355 (intramolecular NH), 3270 br, 3235 sh cm^{-1} (intermolecular HO); c.d. data (*c* 0.7): $\Delta\varepsilon$ 6.28 in water at 210 nm with a shoulder at 225 nm.

Anal. Calc. for $C_{12}H_{22}N_2O_{10}$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.53; H, 6.31; N, 7.87%.

X-Ray structure determination. — The intensities of transparent plate crystals of **1** (0.05 × 0.20 × 0.25 mm^3) were collected on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated CuK_α radiation (λ = 1.54184 Å) at 296(1) K, using the $\omega/2\Theta$ scan technique in the range $1.5<\Theta<75.0°$ with a scan width of $0.40 + 0.14\tan\Theta$. The lattice parameters were determined by least-squares from the setting angles of 25 reflections collected in the range $28<\Theta<30°$. Three standard reflections ($\bar{2}46$, $\bar{1}$,1,18 and 240) were monitored every hour. The intensities of these standards remained constant within experimental error.

Crystal data for **1**. — $C_{12}H_{22}N_2O_{10}$, M_r = 354.32, orthorhombic, space group $C222_1$; a = 6.542(1), b = 7.308(1), c = 30.571(3) Å, V = 1463.7(6) $Å^3$, Z = 4, $F(000)$ = 752. D_x = 1.61 $g.cm^{-3}$, μ(CuK_α) = 11.7 cm^{-1}. A total of 3375 reflections were collected in one half of the limiting sphere. After absorption correction (performed at the end of the isotropic refinement of non-H atoms by the use of the DIFABS program[4]: relative transmission coefficient range from 0.847 to 1.533), merging the four octants of the reciprocal lattice into two, denoted by the *hkl* and *hkl̄* indices, led to 1481 non-zero observations. For the least-squares procedure, 1337 reflections with $I>3\sigma(I)$ were applied. Since MULTAN 82[5] failed to give the correct solution in the space group $C222_1$ (No. 20), the phase problems were solved in a primitive monoclinic cell retaining the space group symmetry $P112_1$ by the use of 495 normalized structure factors $E \geq 1.37$ and 9439 phase relationships. Of the 100 phase sets, No. 95 with probability statistics, ABSFOM 1.02, RESID 16.96, PSIZERO 1.653, led to an E map from which all non-H atoms could be located. The apparent C_2 symmetry of the molecule was then utilized in the refinement procedure by returning to the space group $C222_1$. Hydrogen atoms bound to carbon

atoms were generated from assumed geometries, whereas those belonging to the NH and OH groups were found by $\Delta\rho$ syntheses performed at the end of the isotropic refinement for non-H atoms. Their positions were refined with individual isotropic temperature factors ($B_{iH} = B_{iX} + 1$ Å^2, where X = C, N, O). The refinement of 109 parameters, minimising $\Sigma w(\Delta F)^2$ with the weighting scheme $w = F_o^2/\sigma^2(F_o)^2$ resulted in $R = 0.041$ and $R_w = 0.053$ ($R_{tot} = 0.047$) for the correct enantiomer known from chemical evidence. The highest peak in the final $\Delta\rho$ map was 0.58 e/Å^3.

All calculations were performed on a PDP-11/34 minicomputer with the SDP-package provided by Enraf–Nonius (Delft).

Quantum chemical calculations. — These were carried out by the GEOMO program, completed with gradient optimization procedure on the MINDO/3 level. A full internal co-ordinate system recommended by Pulay *et al.*[6] was used for geometry optimization. The maximum forces in the length and angle co-ordinates of the final optimization were less than 0.005 millidyne.

RESULTS AND DISCUSSION

The solid-state conformation of **1**, computed from the final fractional atomic co-ordinates listed in Table I, is shown in Fig. 1. The bonding interatomic distances, valence angles, and selected torsion angles are given in Tables II–IV*.

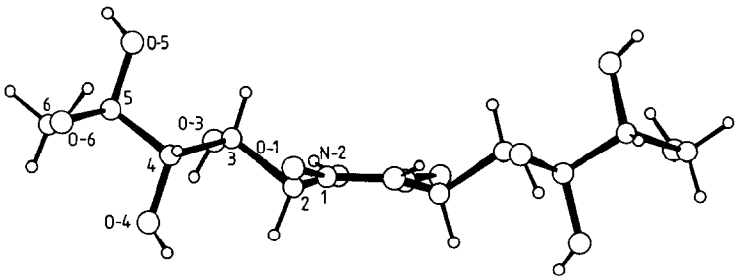

Fig. 1. Calculated projection of a molecule of **1** perpendicular to the *a* axis, with atomic labelling. The H atoms are shown, but not labelled.

The dioxopiperazine ring adopts a flattened boat conformation [puckering parameters[7]: Q = 0.285(2) Å, Φ = 66.7(4)°, Θ = 90.0(4)°] with a C_2 axis perpendicular to its best plane. It is composed of two nearly planar amide groups with a dihedral angle of 22.6(2)°. The torsion angles (using the convention of the IUPAC–IUB Commission on Biochemical Nomenclature[8]) have the following

*Supplementary data have been deposited with, and may be obtained from, Elsevier Science Publishers B.V., B.B.A. Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/408/*Carbohydr. Res.*, 187 (1989) 187–195.

TABLE I

FRACTIONAL CO-ORDINATES ($\times 10^4$ FOR x AND y, AND 10^5 FOR z)[a] AND EQUIVALENT ISOTROPIC TEMPERATURE FACTORS (Å^2)[b] FOR **1**

Atom	x/a	y/b	z/c	B_{eq}
C-1	3138(3)	1350(2)	22426(6)	1.3(6)
C-2	5181(3)	1038(2)	20238(6)	1.3(6)
C-3	5492(2)	2256(2)	16120(6)	1.3(6)
C-4	4176(3)	1731(2)	12195(6)	1.3(6)
C-5	4676(3)	2906(2)	8181(6)	1.5(6)
C-6	3395(3)	2427(3)	4212(6)	2.1(8)
O-1	1566(2)	1527(2)	20225(4)	2.1(5)
N-2	6897(2)	1395(2)	23189(5)	1.7(6)
O-3	7608(2)	2182(2)	15011(4)	1.6(5)
O-4	4581(2)	−109(2)	10919(4)	1.9(5)
O-5	4338(2)	4760(2)	9427(5)	2.0(5)
O-6	1246(2)	2490(2)	5041(4)	2.1(5)

[a]Estimated standard deviations in parentheses. [b]B_{eq} = 4/3*trace (B*G), where G is the direct metric tensor.

TABLE II

BOND LENGTHS (Å) FOR **1**

C-1–O-1	1.236(3)	C-3–C-4	1.526(3)
C-1–C-2	1.512(3)	C-4–O-4	1.427(3)
C-1–N-2′	1.341(3)	C-4–C-5	1.534(3)
C-2–N-2	1.464(3)	C-5–O-5	1.427(3)
C-2–C-3	1.556(3)	C-5–C-6	1.516(3)
C-3–O-3	1.427(2)	C-6–O-6	1.429(3)

TABLE III

BOND ANGLES (DEGREES) FOR **1**

C-2′–N-2′–C-1	126.8(3)
C-2–C-1–O-1	120.7(3)
C-2–C-1–N-2′	117.4(3)
O-1–C-1–N-2′	121.8(3)
C-1–C-2–C-3	112.8(3)
C-1–C-2–N-2	112.2(3)
C-3–C-2–N-2	107.2(3)
C-2–C-3–C-4	114.7(3)
C-2–C-3–O-3	107.3(3)
C-4–C-3–O-3	110.6(3)
C-3–C-4–C-5	111.6(3)
C-3–C-4–O-4	110.3(3)
C-5–C-4–O-4	105.7(3)
C-4–C-5–C-6	113.1(3)
C-4–C-5–O-5	106.6(3)
C-6–C-5–O-5	110.4(3)
C-5–C-6–O-6	113.2(3)

TABLE IV

RELEVANT EXOCYCLIC TORSION ANGLES (DEGREES) FOR **1**

N-2′–C-1–C-2–C-3	−139.1(4)
C-1–C-2–C-3–C-4	−70.8(3)
C-1′–N-2–C-2–C-3	147.9(1)
N-2–C-2–C-3–C-4	165.1(3)
C-2–C-3–C-4–C-5	−176.0(3)
C-3–C-4–C-5–C-6	−179.9(4)
O-1–C-1–C-2–C-3	41.9(3)
O-1–C-1–C-2–N-2	163.2(3)
O-3–C-3–C-2–C-1	165.9(3)
O-3–C-3–C-4–C-5	−54.5(3)
O-4–C-4–C-3–C-2	−58.3(3)
O-4–C-4–C-5–C-6	60.1(3)
O-5–C-5–C-4–C-3	−58.4(3)
O-5–C-5–C-6–O-6	−64.7(3)
O-6–C-6–C-5–C-4	54.7(3)

values: φ = 23.5(4), ψ = −17.8(3), and ω = 5.0(3)°. The corresponding values observed in the analogous *cyclo*(L-Ser-L-Ser)[3] are: φ_1 = −4.0(6)°, ψ_1 = −1.0(6)°, ω_1 = 4.5(7)°, φ_2 = −3.2(6)°, ψ_2 = −1.7(6)°, and ω_2 = 5.4(7)°. The main conformational feature of **1** is the adoption of two intramolecular hydrogen bonds of N–H···O type (C_5-conformation) (Table V). The five-membered hydrogen-bonded rings are non-planar, the torsion angle N-2–C-2–C-3–O-3 = 41.8(3)°. The C-2 atoms bearing the sugar side-chains in pseudo-equatorial positions [the CH_2^{β} groups in *cyclo*(L-Ser-L-Ser) (**2**) are quasi-axial] are situated on the bow and stern of the boat. The backbones of the sugar side-chains are characterized by three internal rotations about the C–C bonds falling invariably in the antiperiplanar range. The fourth, about C-2–N-2, is determined presumably by the intramolecular N-H···O hydrogen bond which fixes the position of the acceptor O-3 in a synclinal position relative to N-2.

The c.d. spectrum of **1** in water shows a positive band at 210 nm ($\Delta\varepsilon$ 6.28)

TABLE V

RESULTS OF THE ENERGY CALCULATION FOR THE MODELS DEPICTED IN FIG. 2 FOR TRUNCATED **1** AND THE ANALOGUE **2**

Type	ΔE *(kcal/mol)*	*Distances (Å)*		*Torsion angles*	
		O-3···O-1	*O-3···N-2*	*N-2–C-2–C-3–O-3*	*C-2–C-3–O-3–H*
NPC_6	14.72	3.11		137.7	0.1
PC_6	6.85	3.20		169.9	58.0
NPC_5	6.06		2.92	−41.8	−77.4
PC_5	2.97		2.73	−24.73	−175.5
NP	1.34			45.8	93.3
P				56.08	88.26

with a shoulder near 225 nm. In the spectrum of **2**, a negative band appears[3] at 207 nm. This result, taking into consideration the opposite configuration of the building units, suggests that, in solution, the two dioxopiperazine derivatives adopt a similar conformation. In order to explore the effect of the five-membered rings closed by NH···O contacts upon the conformational energy, semi-empirical calculations (see Experimental) were performed both on **1** and **2** with the absence and presence of the intramolecular hydrogen bonds as depicted in Fig. 2. Crystallographic data for **2** were used as a trial model for planar non-hydrogen-bonded (P) as well as planar O-H···O (PC_6) and N-H···O (PC_5) hydrogen-bonded conformations. For an appropriate comparison, the atomic co-ordinates of **1** truncated at C-4 (*i.e.*, replaced with H) served as a trial model of the dioxopiperazine ring in the boat conformation (NP). The results of the calculations are summarized in Table V. The minimum energy was found for the planar non-hydrogen-bonded conformation (type P) resembling that of **2** in the solid state[3], which suggests that the same conformational state is favoured, not only in the crystalline form but also in the isolated molecule. Similarly, the folded structure of **1** with no intramolecular hydrogen bond (NP) has low energy. In contrast, all other conformations influenced by intramolecular hydrogen bonds, especially O-H···O (PC_6 and NPC_6), are less stable. The energy of the PC_5 state is 3 kcal/mol lower than that of the corresponding NPC_5 boat conformation of **1**. Presumably, the development of the C_5 conformation (*i.e.*, an N–H···O bonded structure) in the flattened boat form is accompanied by an unfavourable eclipse of the C=O and C^{α}–C^{β} bonds. Furthermore, the flattening of the dioxopiperazine ring increases the distance between the amide hydrogen and the first side-chain oxygen, thus weakening the ring-stabilizing N–H···O interactions. That the boat conformation of **1**, accompanied by intramolecular N-H···O hydrogen-bonds, is also affected by the presence of the sugar side-chains cannot be ignored. However, the specific NH···O^{γ} interactions in folded serine-containing dipeptide models, recognized by solid-state[9] and solution studies[10] *via* a feedback effect, may also be important in systems with longer side-chains containing hydroxyl groups, *e.g.*, a sugar chain in glycoproteins.

Analysis of the molecular packing has shown that the molecules possessing a two-fold axis at (0,*y*,1/4) and at the corresponding symmetry equivalent co-ordinates, respectively, are stretched along the long *c* axis (Fig. 3), thus forming

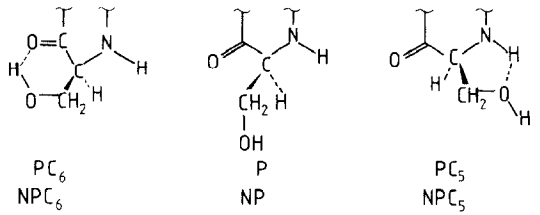

Fig. 2. Atomic moieties used for modelling **1** (NPC_6, NP, NPC_5) and **2** (PC_6, P, PC_5) in semi-empirical energy calculations.

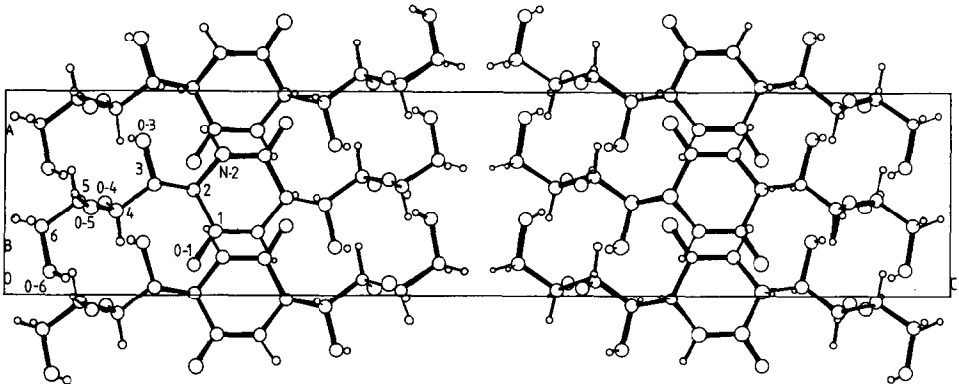

Fig. 3. A perspective view of the molecular packing of **1** in the *ac* plane. The extended molecules form two OH···O hydrogen-bonded bands per unit cell, which are separated by hydrophobic C-6-H···H-C-6 contacts of 2.72(4) and 2.70(4) Å.

two separate 2-dimensional layers which communicate only through (C-6–H···H–C-6) contacts as follows: H-6-A···H-6-A $[x,1-y,\bar{z}]$ 2.72(4) Å; H-6-B···H-6-B $[x,\bar{y},\bar{z}]$ 2.70(4) Å.

Within these layers, there are molecules bonded by intermolecular hydrogen bridges of the OH···O type, resulting in close packing of the sugar side-chains as indicated by the high packing coefficient[11] of 0.81. The volume of the molecule (295.8 Å^3) was calculated from the atomic co-ordinates given in Table I with appropriately fixed X–H distances (where X = C, N, and O) and using the atomic radii recommended by Kitaigorodsky[12] (r_C = 1.80, r_N = 1.58, r_O = 1.52, and r_H = 1.17 Å) by a program written by Mr. Cs. Kertész. This program computes atomic volume increments, taking into account the differences in their hybridizations and environments. Study of the intermolecular close-contacts revealed four hydrogen bonds of the OH···O(H) type (Table VI). In the lattice of **1**, in contrast to the crystal structure of **2**, there is no hydrogen bond with the C=O group acting as acceptor. The four intermolecular hydrogen bonds depicted in Fig. 4, where, for

TABLE VI

PARAMETERS OF INTRA- AND INTER-MOLECULAR HYDROGEN BONDS IN **1**

D^a	A^a	*Acceptor symmetry*	$D\cdots A$ (Å)	$H\cdots O$ (Å)	D-$H\cdots A$ (°)
N-2-H···O-3		x,y,z	3.188(3)	2.23(3)	154(2)
O-3-H···O-5		$x+1/2,y-1/2,z$	2.709(3)	2.00(3)	144(2)
O-4-H···O-3		$x-1/2,y-1/2,z$	2.676(3)	1.83(3)	172(2)
O-5-H···O-6		$x+1/2,y+1/2,z$	2.711(3)	1.84(3)	168(2)
O-6-H···O-4		$x-1/2,y+1/2,z$	2.739(3)	1.89(3)	160(2)

[a]D, donor; A, acceptor.

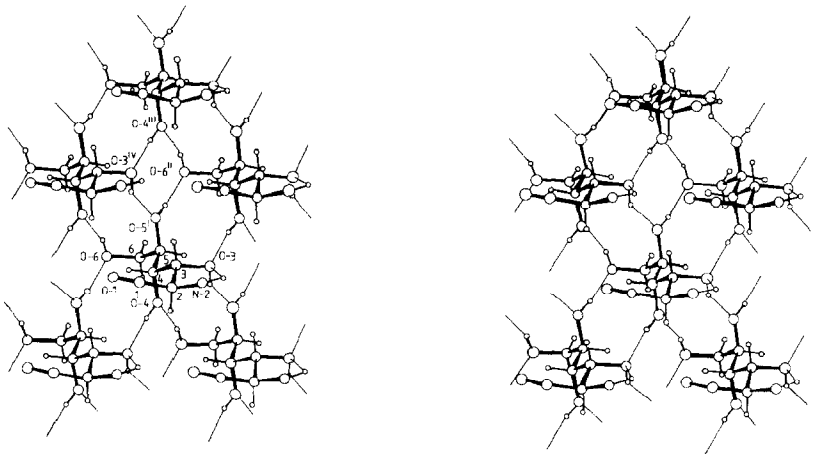

Fig. 4. Stereoscopic representation of the hydrogen bonding developed between the sugar side-chains in **1** viewed down the long *c* axis. In order to provide a clear view, only the C_2 symmetry-free halves of the dimeric molecules are shown with atomic labelling for the unit at (x,y,z) and those of the bridgehead atoms (i, x,y,z; ii, $x + 1/2, y + 1/2, z$; iii, $x,y + 1, z$; iv, $x - 1/2, y + 1/2, z$) in the OH···O contacts. The best plane ($-0.78681X + 0.10734Y - 0.60778Z = -3.58701$) of the square-like four-fold ring of the hydrogen bonds [the average distances of O and H atoms from the best plane are 0.022(2), 0.05(3) Å, respectively] makes a dihedral angle of 37.4(3)° with the *c* axis.

clarity, only the C_2 symmetry-free halves of the molecules are presented, build up an almost rectangular square between each group of four side-chains related by translations along the *a* and *b* axes as follows: 0,0; − 1/2,1/2; 0,1; 1/2,1/2. In these four-fold rings of OH···O bonds, each OH group maintains two hydrogen bonds as donor and acceptor linking together two other side-chains separated by unit translation in either the *a* or *b* direction. Thus, each sugar side-chain participates in eight intermolecular hydrogen bonds donated by four OH···O rings to the hydroxyl groups, respectively. Therefore, each side chain, in accordance with the C-centered orthorhombic unit-cell, is linked twice to each of the four other side-chains translated by ±1/2 of the unit vectors along *a* and *b* axes. This situation provides an optimum of co-operative effect between the hydrogen bonds. Within the side chains, O-3 assumes an antiperiplanar position with O-6, whereas O-4 keeps the same arrangement with O-5. The corresponding torsion angles are O-6···C-5–C-4···O-3 179.4(3)°, O-5–C-5–C-4···O-3 −85.0(3), O-6···C-5–C-4–O-4 86.0(2), O-5–C-5–C-4–O-4 −178.4(3).

These two pairs of groups are almost perpendicular to each other, resulting in a three-dimensional cross formed around the C-4–C-5 bond. The longer O-3···O-6 arm is almost parallel with the *a* axis, whereas the O-4···O-5 arm follows direction *b*. Together, these account for the close packing of the sugar side-chains, which is repeated on the other side of the molecules by their two-fold symmetry axes forming infinite bands of hydrogen-bonded molecules along the *ab* plane.

This enforced molecular packing maintained by the parallel sugar side-chains

may also account for the rapid formation of **1**. Thus, **2** could be obtained from L-serine methyl ester hydrochloride[13] only in the presence of 1 equiv. of sodium methoxide. No dioxopiperazine ring was formed in the presence of a weaker tertiary base under conditions which were favourable for the cyclization of methyl 2-amino-2-deoxy-D-gluconate to give **1**. Similarly, no cyclic product was formed from 2-amino-2-deoxy-D-gluconolactone. The apparent contradiction between these observations and data in the literature[14] (*i.e.*, increasing side-chain decreases the affinity of cyclization) can be resolved, however, if the enhanced rate of cyclization of methyl 2-amino-2-deoxy-D-gluconate is attributed to the catalytic effect of HO-3 and to the orienting effect of the strong molecular associations formed between the neighbouring parallel sugar chains held together by the four-fold OH···O hydrogen-bond rings (Fig. 4). This pattern strongly suggests that two-dimensional networks of hydrogen-bonded molecules are also present in solution and assist in fixing the orientations of adjacent molecules, which promotes dimerization to yield **1**.

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