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Molecular Recognition in Polyols: the Structure of L-Mannonic Acid Hydrazide Revealing a Common Packing Motif in Different Acyclic Sugars

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Abstract

$C_6H_{14}N_2O_6$, $M_r = 210.19$, tetragonal, $P4_3$, $a = 4.938\ (1)$, $c = 36.907\ (8)$ Å, $V = 899.93$ Å^3, $Z = 4$, $D_x = 1.551$ g cm^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 12.18$ cm^{-1}, $F(000) = 448.0$, $T = 295$ K, final $R = 0.032$ and $wR = 0.029$ for 759 observed reflections. The sugar chain of L-mannonic acid hydrazide shows the expected all-*trans* conformation. The hydrogen-bond pattern includes a homodromic cycle with a special connectivity that is also realized in several other open-chain sugar derivatives with different chirality. The relationship between the dimensions of the crystal lattice and the occurrence of this special cycle is discussed.

Introduction

There is a steadily growing interest in the principles that govern the packing arrangement of a compound in its crystalline state. This interest originates on the one hand from the desire to design crystals with non-linear optical and magnetic properties or unusual conductance (DiSalvo, 1990) or to use them for stereo-controlled organic reactions (Desiraju, 1984). On the other hand, the information on molecular recognition in the solid state gained from small molecules might be transferable to larger molecules of biological importance, *e.g.* proteins. In crystal engineering, the critical point is to direct molecules into appropriate juxtaposition, which requires a good knowledge of the packing principles of the compound class considered. Studies using the wealth of information in the Cambridge Structural Database (Allen *et al.*, 1979) and/or systematic calculations (Higgins, 1989*a*,*b*) might thus be the prerequisite for successful crystal engineering. A packing analysis of hydrocarbons containing one C=O or C=N group has, for example, been performed by Gavezotti (1990) who found that the dipole–dipole interaction is only weak and might easily be overcome by other cohesive forces. In an exceptional case, the so-called chloro- or β-steering effect (Desiraju, 1987) – *i.e.* the influence of chlorine atoms that are bound to aromatic ring systems on the packing mode in the crystalline state – has been used without knowledge of its precise nature in early applications to yield crystals in which topochemical cycloadditions could be performed (Green & Schmidt, 1970; Elgavi, Green & Schmidt, 1973).

The power of hydrogen bonds to direct desired packing arrangements in molecular crystals has also been recognized and has been applied successfully to the controlled assembly of molecular sheets (Garcia-Tellado, Geib, Goswami & Hamilton, 1991). Detailed investigations have been made on the packing characteristics of amide and carboxyl groups (Berkovitch-Yellin & Leiserowitz, 1980, 1982; Berkovitch-Yellin, Ariel & Leiserowitz, 1983). Etter (1990) used graph sets in order to identify hydrogen-bond arrangements that are preferred by certain functional groups. Five classes were proposed for the crystal structures of phenols on the basis of their hydrogen-bond patterns (Perrin, Lamartine, Perrin & Thozet, 1987).

So far, polyols have not attracted interest as potential tools in crystal engineering. However, the aggregation behaviour of the amphiphilic *N*-(*n*-alkyl)-D-aldonamides has been studied in detail in order to investigate their aptitude (i) as structural models for biological membranes and (ii) as scaffoldings for synthetic functional systems (Fuhrhop, Schnieder, Rosenberg & Boekema, 1987; Fuhrhop, Schnieder, Boekema & Helfrich, 1988; Fuhrhop & Boettcher, 1990; Fuhrhop, Svenson, Boettcher, Rössler & Vieth, 1990). Both *N*-(*n*-decyl)-D-ribonamide (Tinant, Declercq & Van Meerssche, 1986) and the *N*-(*n*-alkyl)-D-gluconamides (Müller-Fahrnow, Hilgenfeld, Hesse, Saenger & Pfannemüller, 1988; Zabel *et al.*, 1986; Jeffrey & Maluszynska, 1990) display an unusual head-to-tail molecular arrangement in their crystal structures, whereas *N*-(*n*-octyl)-D-gulonamide (André, Luger, Svenson & Fuhrhop, 1992*a*) and *N*-(*n*-octyl)-D-talon-

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amide (André, Luger, Svenson & Fuhrhop, 1992*b*) show the tail-to-tail bilayer packing usually found in amphiphilic compounds (Pascher & Sundell, 1977; Harlos, Pascher & Sundell, 1984).

A great deal of structural data is also available for other open-chain sugars as the conformational behaviour of different derivatives in the solid and solvated states has been studied intensively. Until recently, it was widely accepted that 1,3-syndiaxial interactions determined the crystal conformation of alditols (Jeffrey & Kim, 1970) and other acyclic sugar derivatives. Deviations from an extended sugar chain were expected to occur when such a planar zigzag conformation would give rise to the existence of two parallel carbon–oxygen bonds ('O//O' interaction) or a carbon–carbon parallel to a carbon–oxygen bond ('C//O' interaction) (Jeffrey & Kim, 1970). This hypothesis was challenged recently by the observation of many unexpected 1,3-*syn* interactions in novel crystal structures of alditols (Angyal, Saunders, Grainger, Le Fur & Williams, 1986; Köll, Komander, Angyal, Morf, Zimmer & Kopf, 1991) and nitro-alditols (Kopf, Brandenburg, Seelhorst & Köll, 1990; Köll, Malzahn & Kopf, 1990).

This work is part of our comparative studies on the packing and conformational behaviour of derivatized acyclic sugars (André, Luger, Svenson & Fuhrhop, 1992*a*,*b*). A common packing arrangement for different open-chain sugars is represented here.

Experimental

L-Mannonic acid hydrazide was prepared by reaction of L-mannonic acid γ-lactone with hydrazine in 95% ethanol, following a procedure for the corresponding *gluco* derivative according to Van Marle (1920); single crystals of the title compound were produced by direct evaporation from the reaction solution. The crystal size of the measured specimen was 0.43 × 0.40 × 0.09 mm. Lattice parameters were obtained from least-squares refinement of 36 reflections with $50 < 2\theta < 75°$. At room temperature two octants of dependent reflections were measured in the ω–2θ-scan mode up to $(\sin\theta/\lambda)_{max} = 0.583$ Å^{-1} with Ni-filtered Cu $K\alpha$ radiation on a Stoe four-circle diffractometer. 1681 reflections, one unobserved with $F < 2\sigma(F)$; h, k, l 0 to 5, −5 to 5, 0 to 42. Three standard reflections ($1\bar{3}7$,$2\bar{2}6$, $1,2,\bar{1}1$) measured every 45 min showed insignificant intensity variation during the data collection. Lorentz–polarization, but no absorption correction applied. Merging gave a unique data set of 759 reflections ($R_{int} = 0.76\%$, $R_\sigma = 0.68\%$). The only systematically absent reflections found for $00l$, $l \neq 4n$, indicated the possible space groups $P4_1$, $P4_3$, $P4_122$ and $P4_322$. The latter two would require the molecule to have a twofold symmetry axis which is impossible in the present case. In both $P4_1$ and $P4_3$, structure solution was easily obtained with *SHELXS*86 (Sheldrick, 1985). Only the $P4_3$ structure refinement ran satisfactorily with the correct L-enantiomer, thereby indicating that this is the correct space group.

Conventional full-matrix least-squares refinement of atomic positional and thermal parameters, scale factor and an isotropic extinction parameter were carried out with the *XTAL* system (Hall & Stewart, 1987), the quantity minimized was $\sum w(|F_o| - |F_c|)^2$, $w = 1/\sigma^2(F)$, with $\sigma^2(F)$ values from counting statistics.

All non-H atoms were refined with anisotropic thermal parameters; all H atoms were located in difference Fourier maps and refined with isotropic thermal parameters. Final $R = 0.032$ and $wR = 0.029$, based on 759 merged observed reflections and 183 variables, goodness of fit $S = 5.83$, largest peak in final difference map = 0.258, largest hole = −0.151 e Å^{-3}. Atomic scattering factors for C, O and N atoms were taken from Cromer & Mann (1968) and the H-atom scattering factors of Stewart, Davidson & Simpson (1965) were used.

Discussion

Molecular structure

Final atomic coordinates and equivalent isotropic displacement factors (Hamilton, 1959) are given in Table 1.* An *ORTEP* representation (Johnson, 1976) of the title compound is shown in Fig. 1, which also gives the atomic numbering scheme. Table 2 lists bond lengths and bond and torsion angles.

The C—C and C—O(H) bond lengths are 1.508–1.526 and 1.423–1.438 Å, respectively, with mean values of 1.518 and 1.429 Å, being of the same magnitude as the corresponding bonds in the X-ray crystal structures of alditols (Jeffrey & Kim, 1970). The C—C bond lengths show a slight shortening towards the end of the chain usually observed in alditols and are probably an effect of the atomic thermal motion (Jeffrey & Kim, 1970). There is also a shortening in the C(1)—N(1) and N(1)—N(2) bonds in the title compound compared to isonicotinic acid hydrazide [1.314 (4) compared to 1.346 (5) Å and 1.405 (5) to 1.428 (5) Å respectively (Bhat, Singh & Vijayan, 1974)]. The carbonyl bond, however, is longer in the title compound [1.251 (4) compared to 1.235 (4) Å].

* Lists of observed and calculated structure factors, anisotropic displacement factors and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55706 (9 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CR0432]

Table 1. *Atomic coordinates and equivalent isotropic displacement parameters* ($Å^2 \times 10^2$)

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

	x	y	z	U_{eq}/U
C(1)	0.7376 (6)	0.6900 (6)	0.0272	2.52 (9)
O(1)	0.5835 (5)	0.8733 (4)	0.0161 (1)	3.18 (7)
C(2)	0.6553 (6)	0.4998 (6)	0.0576 (1)	2.36 (8)
O(2)	0.4239 (5)	0.3464 (5)	0.0466 (1)	3.06 (7)
C(3)	0.5785 (6)	0.6634 (6)	0.0911 (1)	2.32 (8)
O(3)	0.7930 (5)	0.8501 (5)	0.0984 (1)	2.71 (7)
C(4)	0.5159 (7)	0.4846 (6)	0.1236 (1)	2.54 (8)
O(4)	0.7507 (5)	0.3327 (5)	0.13324 (9)	2.98 (7)
C(5)	0.4358 (6)	0.6467 (6)	0.1569 (1)	2.49 (9)
O(5)	0.2029 (5)	0.8000 (5)	0.1473 (1)	3.22 (8)
C(6)	0.3751 (7)	0.4726 (7)	0.1895 (1)	3.1 (1)
O(6)	0.1627 (5)	0.2804 (4)	0.1825 (1)	3.21 (7)
N(1)	0.9747 (6)	0.6474 (6)	0.0121 (1)	3.24 (8)
N(2)	1.0619 (6)	0.7881 (7)	−0.0189 (1)	3.6 (1)
H(2)	0.826 (7)	0.380 (7)	0.0632 (9)	2.6 (9)
H(4)	0.374 (7)	0.377 (8)	0.119 (1)	3 (1)
H(3)	0.409 (9)	0.746 (7)	0.085 (1)	4 (1)
H(5)	0.595 (6)	0.777 (7)	0.1631 (9)	1.7 (8)
H(61)	0.316 (6)	0.577 (6)	0.2116 (8)	1.4 (8)
H(62)	0.533 (9)	0.355 (8)	0.197 (1)	4 (1)
H(O2)	0.46 (1)	0.19 (1)	0.036 (1)	10 (2)
H(O3)	0.877 (8)	0.784 (7)	0.114 (1)	2.0 (9)
H(O4)	0.764 (8)	0.199 (8)	0.125 (1)	3 (1)
H(O5)	0.210 (9)	0.913 (9)	0.161 (1)	5 (1)
H(O6)	0.036 (9)	0.356 (8)	0.167 (1)	5 (1)
H(N1)	1.088 (9)	0.52 (1)	0.022 (1)	6 (1)
H(N21)	1.217 (9)	0.88 (1)	−0.009 (1)	6 (1)
H(N22)	0.935 (8)	0.937 (8)	−0.023 (1)	4 (1)

Table 2. *Bond lengths* (Å) *and bond and torsion angles* (°)

C(1)—O(1)	1.251 (4)	C(1)—C(2)	1.518 (4)
C(1)—N(1)	1.314 (4)	C(2)—O(2)	1.429 (4)
C(2)—C(3)	1.526 (5)	C(3)—O(3)	1.430 (4)
C(3)—C(4)	1.521 (6)	C(4)—O(4)	1.426 (4)
C(4)—C(5)	1.519 (6)	C(5)—O(5)	1.423 (4)
C(5)—C(6)	1.508 (6)	C(6)—O(6)	1.438 (4)
N(1)—N(2)	1.405 (5)		

O(1)—C(1)—C(2)	121.7 (3)	O(1)—C(1)—N(1)	121.3 (3)
C(2)—C(1)—N(1)	116.9 (3)	C(1)—C(2)—O(2)	109.5 (3)
C(1)—C(2)—C(3)	109.8 (3)	O(2)—C(2)—C(3)	108.1 (3)
C(2)—C(3)—O(3)	108.1 (3)	C(2)—C(3)—C(4)	112.5 (3)
O(3)—C(3)—C(4)	112.1 (3)	C(3)—C(4)—O(4)	109.7 (3)
C(3)—C(4)—C(5)	112.7 (3)	O(4)—C(4)—C(5)	106.7 (3)
C(4)—C(5)—O(5)	106.7 (3)	C(4)—C(5)—C(6)	113.4 (3)
O(5)—C(5)—C(6)	110.0 (3)	C(5)—C(6)—O(6)	112.3 (3)
C(1)—N(1)—N(2)	122.6 (3)		

C(1)—C(2)—C(3)—C(4)	−175.3 (3)	O(1)—C(1)—C(2)—O(2)	62.5 (5)
C(2)—C(3)—C(4)—C(5)	−179.3 (3)	O(2)—C(2)—C(3)—O(3)	−170.4 (3)
C(3)—C(4)—C(5)—C(6)	−179.5 (4)	O(3)—C(3)—C(4)—O(4)	−60.0 (4)
C(2)—C(1)—N(1)—N(2)	172.5 (3)	O(4)—C(4)—C(5)—O(5)	179.5 (3)
O(5)—C(5)—C(6)—O(6)	61.6 (4)	N(1)—C(1)—C(2)—O(2)	−115.1 (3)
N(1)—C(1)—C(2)—C(3)	126.3 (3)	O(1)—C(1)—N(1)—N(2)	−5.1 (5)

As the single bond between the hydrazide moiety and the pyridine ring of the isonicotinic derivative excludes an interaction of their π systems, the geometry of the hydrazide group should be identical in both compounds, unless additional effects are present. In fact, the different C=O and C—N bond lengths in the two hydrazide derivatives can be attributed to different environments at the amide unit (Jeffrey, Ruble, McMullan, DeFrees & Pople, 1981): the carbonyl O atom of isonicotinic acid hydrazide does not participate in the hydrogen-bonding scheme whereas it accepts three hydrogen bonds in the title compound.

As can be expected for an acyclic sugar undisturbed by 1,3-*syn* interaction (Jeffrey & Kim, 1970), the carbon chain of L-mannonic acid hydrazide adopts an extended all-*trans* conformation in the crystal. It has been reported that this zigzag conformation is also strongly favoured in solutions of D-mannonic acid ethyl ester (Horton, Wałaszek & Ekiel, 1983) and D-mannononitrile 2,3,4,5,6-pentaacetate (Seldes, Gros, Thiel & Deferrari, 1975). On the other hand, non-negligible populations of non-linear conformers were calculated for the latter compound in a recent molecular mechanics study (Lòpez-Calahorra, Velasco, Castells & Jaime, 1990). The motility of the solvated sugar was demonstrated, too, by a molecular dynamics simulation of mannitol in water, where the torsion angles exhibited large fluctuations (Grigera 1988, 1990).

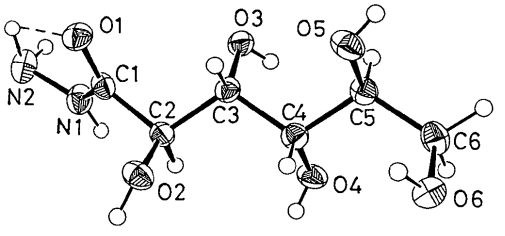

Fig. 1 Conformation and atomic numbering scheme of L-mannonic acid hydrazide (thermal ellipsoids refer to 50% probability).

There are crystal structures where a *manno*-configurated sugar chain exceptionally adopts a bent conformation in solid state, thereby *generating* 1,3-*syn* interactions. This unusual behaviour is enforced in *N*-(*p*-bromobenzyl) nogalonamide (Wiley, Duchamp, Hsiung & Chidester, 1971) by a strong intramolecular hydrogen bond between the carbonyl O atoms and the only unmethylated hydroxyl group; in the crystal structure of a mannitolatodimolybdate complex (Hedman, 1977), the mannitol moiety retains the sickle conformation that it presumably adopts in its complex in solution (Chapelle & Verchère, 1991; Matulová, Bílik & Alföldi, 1989).

In the crystal structure of 1-*O*-(α-D-glucopyranosyl)-D-mannitol dihydrate (Lindner & Lichtenthaler, 1981) both terminal O atoms lie in the plane of the carbon chain. This does not hold for the corresponding O atoms of the title compound. The bond between C(6) and the terminal O atom O(6) is not a linear extension of the zigzag chain in L-mannonic acid hydrazide, but makes a torsion angle in the $-sc$ range. The conformation, therefore, is the same as in the *p*-bromophenylhydrazone of D-mannose (Furberg & Solbakk, 1969), DL-mannitol (Kanters, Roelofsen & Smits, 1977), the polymorphs of D-mannitol (Berman, Jeffrey & Rosenstein, 1968; Kim, Jeffrey & Rosenstein, 1968) and 1-deoxy-1-nitro-L-*manno*-hexitol (Kopf, Brandenburg, Seelhorst & Köll, 1990).

Table 3. *Hydrogen bonds in* L-*mannonic acid hydrazide*

D—H···*A*	*D*···*A*	*D*—*H*	*H*···*A*	H···*A**	*D*—H···*A*	*D*—H···*A**	Symmetry operation for *A*
N(1)—H(N1)···O(2)	2.959 (4)	0.91 (5)	2.08 (5)	2.02	162 (4)	161	$1+x, y, z$
N(2)—H(N21)···O(1)	2.912 (4)	0.95 (5)	2.04 (5)	2.02	152 (4)	152	$1+x, y, z$
N(2)—H(N22)···O(1)	2.725 (4)	0.98 (4)	2.28 (4)	2.28	107 (3)	107	x, y, z
N(2)—H(N22)···O(6)	3.081 (5)	0.98 (4)	2.25 (4)	2.26	142 (3)	142	$1-y, 1+x, -\frac{1}{4}+z$
O(2)—H(O2)···O(1)	2.710 (4)	0.88 (6)	1.84 (6)	1.75	173 (6)	173	$x, -1+y, z$
O(3)—H(O3)···O(5)	2.720 (4)	0.78 (4)	2.03 (4)	1.87	148 (3)	145	$1+x, y, z$
O(4)—H(O4)···O(3)	2.715 (4)	0.74 (4)	1.98 (4)	1.75	176 (4)	176	$x, -1+y, z$
O(5)—H(O5)···O(6)	2.713 (4)	0.75 (5)	2.00 (5)	1.79	160 (5)	158	$x, 1+y, z$
O(6)—H(O6)···O(4)	2.741 (4)	0.93 (4)	1.88 (4)	1.85	153 (4)	152	$-1+x, y, z$

* Values obtained after *D*—H distances were normalized to a standard distance of 0.97 Å.

Hydrogen-bonding scheme

All hetero atoms are involved in a dense hydrogen-bonding network (Table 3, Figs. 2 and 3). Except for the intramolecular hydrogen bonds, all *D*—H···*A* angles are larger than 140°; the *D*···*A* distances range from 2.710 to 3.081 Å, two thirds of them lying below 2.75 Å. All O atoms act at least once, O(6) twice and O(1) three times as a hydrogen-bond acceptor. Only one H atom, namely H(N22), interacts with two acceptor atoms. It forms an intramolecular hydrogen bond with O(1) and an intermolecular hydrogen bond with $O(6)_{1-y,1+x,-0.25+z}$ thereby producing the only intermolecular hydrogen bond in the *c*-axis direction.

With respect to the common acceptor atom O(1) the three angles *D*—H···O(1) – being 107 (3), 152 (4) and 173 (6)°, respectively – do not differ as markedly as in the crystal structures of L-glutamic acid hydrochloride and L-cysteic acid monohydrate (Jeffrey & Mitra, 1984) where three acceptor atoms share the same H atom. The angles H···O(1)···H in the title compound amount to 308° indicating a flat trigonal pyramid geometry with O(1) on top.

A quadrilateral homodromic cycle (Saenger, 1979) is formed by $O(6)—H(O6)_{x,y,z} \rightarrow O(4)—H(O4)_{-1+x,y,z} \rightarrow O(3)—H(O3)_{-1+x,-1+y,z} \rightarrow O(5)—H(O5)_{x,-1+y,z} \rightarrow O(6)—H(O6)_{x,y,z}$ (Fig. 3). Quadrilateral hydrogen-bond cycles have also been reported for the *p*-bromophenylhydrazone of D-mannose and D-dibromomannitol (Simon & Sasvári, 1973) and for the *B* and *K* forms of D-mannitol but not for the racemate of mannitol and for 1-deoxy-1-nitro-L-*manno*-hexitol. In DL-mannitol the hydrogen-bonding scheme consists of infinite chains formed by O(1)→O(2)→O(3)→O(4)→O(5)→O(6)→O(1) and of finite [O(2)→O(3)→O(4)→O(5)→O(6)→O(12)] and infinite chains [O(2)→O(3)→O(2)] in 1-deoxy-1-nitro-L-*manno*-hexitol where the chains share the same O atoms O(2) and O(3). The occurrence of a quadrilateral hydrogen-bond cycle was derived from oxygen–oxygen distances in the case of the *p*-bromophenylhydrazone of D-mannose,

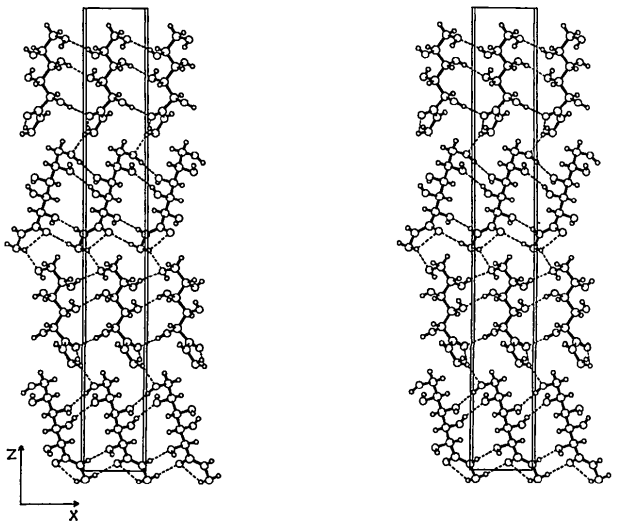

Fig. 2. *SCHAKAL* stereo plot (Keller, 1989) of the molecular packing of L-mannonic acid hydrazide, viewed along the *b* axis. The molecules in the unit cell refer to the following symmetry operations (from top to bottom): $1-y, 1+x, \frac{3}{4}+z$; $1-x, 2-y, \frac{1}{2}+z$; $y, 1-x, \frac{1}{4}+z$; and x, y, z.

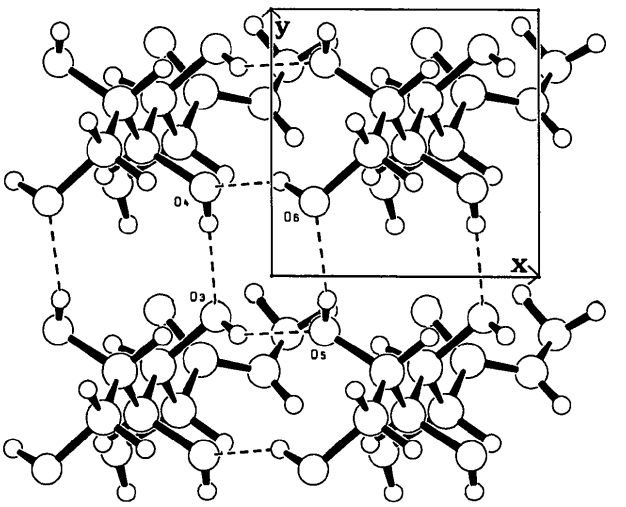

Fig. 3. Quadrilateral homodromic hydrogen-bond cycle in the crystal structure of L-mannonic acid hydrazide. The view is in the negative *c*-axis direction; for clarity, only the asymmetric unit and three of its neighbouring molecules are drawn.

since no H-atom position could be located in that structure analysis. Most remarkably, both the *p*-bromophenylhydrazone derivative and L-mannonic acid hydrazide form this cycle with exactly the same atoms and the same connectivity as *N*-(*n*-alkyl)-D-gluconamides (Jeffrey, 1990*a*) and 1-deoxy-(*N*-methylalkanamido)-D-glucitols with an odd-numbered alkyl chain (Müller-Fahrnow, Zabel, Steifa & Hilgenfeld, 1986; Jeffrey & Maluszynska, 1989; Jeffrey, 1990*a*). As in the title compound the cycle direction is O(3)→O(5)→O(6)→O(4)→O(3) in the gluconamides, but it is reversed in the glucitol compounds (Fig. 4).

Considering this observation, it becomes impossible to determine unambiguously the direction of the homodromic cycle in the *p*-bromophenylhydrazone of D-mannose.

There are no other mannose derivatives that exhibit this quadrilateral cycle built up by the four terminal hydroxyl groups. Since three of their O atoms are bound to chiral C atoms, comparable hydrogen-bonding patterns may occur in crystal structures of the pentose with the same configuration at its three chiral C atoms, *i.e.* arabinose.

Most interestingly, the hydrogen-bond patterns of DL-arabinitol (Hunter & Rosenstein, 1968) and DL-mannitol – consisting of infinite chains – are similar as discussed by Kanters, Roelofsen & Smits (1977). The stereochemical relationship between arabinose and mannose that might be the reason for the similar crystalline behaviour of their racemic alditols has, however, not been recognized.

1-Deoxy-1-nitro-D-*arabino*-pentitol (Kopf, Brandenburg, Seelhorst & Köll, 1990) and *anti*-D-arabinose oxime (Mostad, 1978) both build up this quadrilateral motif. Moreover, the cycle can even be found in the crystal structure of D-altritol, where it is formed exclusively by hydroxyl groups bonded to intra-chain C atoms (Kopf, Bischoff & Köll, 1991). The cycle is built up again by the four terminal hydroxyl groups in *N*-(*n*-decyl)-D-ribonamide (Jeffrey, 1990*a*).

Acyclic sugars *with different chirality* crystallizing in *different space groups* are thus found to form a hydrogen-bond pattern with the same atoms. Except for a short mention in Jeffrey (1990*a*), this has never been discussed in detail.

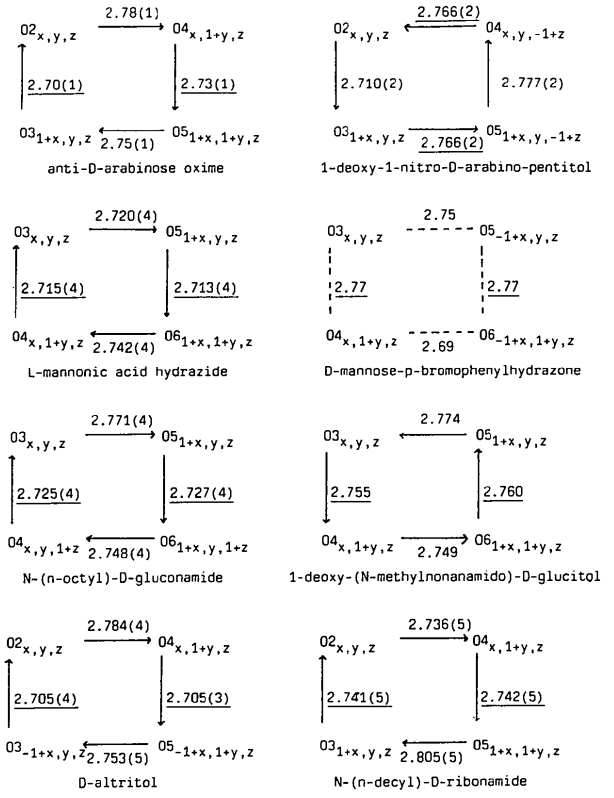

Fig. 4. Homodromic cycles in open-chair sugar derivatives. Dashed lines indicate that the cycle was formulated on the basis of oxygen–oxygen distances only; arrows show the direction of the cycle as derived from refined H-atom positions. Underlined distances indicate that the oxygen–oxygen distances are virtually identical. Only one amphiphilic gluconamide and glucitol is shown, as they are representative of the other members of their families. A representation of the hydrogen-bonding schemes of all gluconamides and glucitols is given by Jeffrey (1990*a*).

Common packing motif

Fig. 4 displays the topology of the homodromic cycles in the different sugars. It can be seen that there is little variation in the oxygen–oxygen distances and that there are two oxygen–oxygen distances in each cycle, lying on opposite sides of the homodromic 'square', which are equal to within three standard deviations. The O atoms building up the cycles belong to molecules which are symmetry related *solely by lattice translations.*

The general connectivity is O(x)—O(x + 2)—O(x + 3)—O(x + 1)—O(x) with x being the number of the lowest numbered O atom involved in the cycle. Both the counter- and clockwise directions are realized for the homodromic arrangements.

The hydroxyl groups taking part in these arrangements are aligned on an extended segment of the carbon chain. Simplifying the nomenclature of Mills (1974), the conformation of the hydroxyl groups is *MAP* for the L- and *PAM* for the D-configurated sugar derivatives, *i.e.* it is identical for all compounds with the two lower numbered hydroxyl groups on one side and the two higher numbered ones on the other side of the straight segment of the carbon chain. This identity is, of course, a necessary condition for the identity of the hydrogen-bond connectivity.

Table 4. *Open-chain sugar derivatives forming homodromic hydrogen-bonding arrangements*

Name	Configuration*	Lattice constants (Å, °)	Space group	Z	Refcode†
L-Mannonic acid hydrazide	AD*DLLA*	$a = 4.938$ (1), $c = 36.907$ (8)	$P4_3$	4	—
D-Mannose *p*-bromophenyl-hydrazone	AL*LDDA*	$a = 4.750$ (6), $b = 5.685$ (7), $c = 13.584$ (2) $\alpha = 100.48$ (1), $\beta = 92.13$ (9), $\gamma = 107.1$ (1)	$P\bar{1}$	1	MANBPH
1-Deoxy-1-nitro-D-*arabino*-pentitol	AL*LDDA*	$a = 4.858$ (1), $b = 13.500$ (1), $c = 6.077$ (1) $\beta = 91.73$ (1)	$P2_1$	2	JERHET
anti-D-Arabinose oxime	A*LDDA*	$a = 4.898$ (2), $b = 5.160$ (3), $c = 14.436$ (7) $\beta = 90.98$ (4)	$P2_1$	2	AARBOX
D-Altritol	A*LDDDA*	$a = 4.901$ (1), $b = 5.175$ (1), $c = 16.258$ (5) $\beta = 97.18$ (2)	$P2_1$	2	—
N-(*n*-Heptyl)-D-gluconamide	AD*LDDA*	$a = 5.183$ (7), $b = 16.18$ (1), $c = 4.803$ (5) $\alpha = 94.2$ (1), $\beta = 96.1$ (1), $\gamma = 99.0$ (1)	$P\bar{1}$	1	FAKGAZ01
N-(*n*-Octyl)-D-gluconamide	AD*LDDA*	$a = 5.252$ (1), $b = 32.426$ (9), $c = 4.805$ (1) $\beta = 94.96$ (5)	$P2_1$	2	FAKFUS
N-(*n*-Undecyl)-D-gluconamide	AD*LDDA*	$a = 5.2267$ (6), $b = 19.628$ (9), $c = 4.7810$ (4) $\alpha = 93.23$ (2), $\beta = 95.60$ (1), $\gamma = 89.58$ (2)	$P\bar{1}$	1	—
1-Deoxy-(*N*-methylnonan-amido)-D-glucitol	AD*LDDA*	$a = 4.985$ (2), $b = 5.603$ (2), $c = 17.449$ (7) $\alpha = 85.4$ (3), $\beta = 86.0$ (3), $\gamma = 76.2$ (3)	$P\bar{1}$	1	FALKAE
1-Deoxy-(*N*-methylundecan-amido)-D-glucitol	AD*LDDA*	$a = 4.950$ (1), $b = 5.6027$ (8), $c = 19.162$ (4) $\alpha = 83.19$ (2), $\beta = 89.76$ (2), $\gamma = 76.28$ (2)	$P\bar{1}$	1	KANTOI
N-(*n*-Decyl)-D-ribonamide	A*DDDA*	$a = 4.825$ (1), $b = 5.452$ (2), $c = 16.100$ (5) $\alpha = 87.08$ (3), $\beta = 93.10$ (2), $\gamma = 96.10$ (2)	$P\bar{1}$	1	DOHHIR

* A, D and L denote carbon atoms that are achiral, and in D and L configurations, respectively; italic letters denote carbon atoms the hydroxyl groups of which are involved in the quadrilateral cycle.

† Taken from the Cambridge Structural Database (Allen *et al.*, 1979).

It can be shown that there is a relationship between the dimensions of the lattice constants and the homodromic cycle formed by the lattice-translation-related molecules. Tables 4 and 5 display the lattice constants and space groups of the compounds forming this special cycle (group I) and of arabinose and mannose derivatives which prefer other patterns (group II).

There is always only one molecule in the asymmetric unit in group I whereas two molecules per asymmetric unit may occur in group II. In group I, we find with no exception only space groups that exhibit at most one screw axis as their symmetry operation. The direction of the screw axis is either perpendicular to the longest lattice constant or parallel to it and the molecules related by the screw axis always point at each other with their short molecular axis. The possible contacts between these molecules – if any – are thereby restricted. All members of group I have two approximately 5 Å long lattice constants and virtually rectangular lattices. The molecules involved in the homodromic cycle are translated along these 5 Å axes as can seen by comparison between Fig. 4 and Table 4. Two subgroups can be formed in group I on the basis of their stereo chemical relationships: *arabino, manno* and *gluco* derivatives share the same stereochemistry along the four terminal C atoms. On the other hand, D-ribose can be regarded as a 'pseudo-enantiomer' of D-talose since the configuration from C(2) to C(4) is opposite to that of the corresponding positions in the latter sugar. The conformational changes needed to adjust the *PAM* conformation are congruent within the sub-groups: an extended sugar chain results in the *PAM* conformation with the *arabino, manno* and *gluco* derivatives whereas the sugar chain must adopt a bent conformation in D-altritol and *N*-(*n*-decyl)-D-ribonamide to bring the four hydroxyl groups into appropriate positions.

The orthorhombic space group $P2_12_12_1$, which is found exclusively in group II, implies multiple hydrogen bonding between the molecules related to each other by the screw axes. No quadrilateral cycle will therefore be built up by lattice-translation-related molecules. This, of course, does not rule out quadrilateral hydrogen-bond cycles of different type that are found, for example, in the crystal structures of the polymorphs of D-mannitol and D-dibromomannitol (all in group II). The other members of group II form finite and infinite hydrogen-bond chains.

In the crystal structure of D-dibromomannitol there are *two* molecules in the asymmetric unit and both of them are involved in a non-group I cycle. Most remarkably, the four *terminal* hydroxyl groups form quadrilateral cycles in the *B* and *K* forms of D-mannitol where only one molecule per asymmetric unit is found. But compared to the mannose derivatives of group I, the connectivity is different: it is O(3)→O(4)→O(5)→O(6)→O(3) in the *B* form and the sense of direction is reversed in the *K* form [see Figs. 3 and 4 of Kim, Jeffrey & Rosenstein (1968)]. Moreover, the cycle is built by molecules related by both a screw axis and a lattice translation.

1-Deoxy-1-nitro-L-*manno*-hexitol of group II also shows two 5 Å lattice constants but it crystallizes in a hexagonal space group with an angle of 120°. This seems to prevent the formation of the group I cycle.

It can now be concluded that the existence of two 5 Å lattice constants within a near-rectangular lattice and the occurrence of only one molecule per asymmetric unit are associated with the existence of a

Table 5. *Open-chain arabino- and manno-derivatives (group II)*

Name	Lattice constants* (Å, °)	Space group	Z	Refcode†
D-Arabinitol‡	$a = 4.823$ (1), $b = 7.675$ (1) $c = 9.705$ (1), $\alpha = 96.13$ (1) $\beta = 96.04$ (1), $\gamma = 106.82$ (1)	$P1$	2	—
DL-Arabinitol	$a = 9.213$ (1), $b = 4.855$ (2) $c = 15.490$ (2)	$Pna2_1$	4	ARABOL
syn-D-Arabinose oxime§	$a = 4.708$ (1), $b = 8.955$ (4) $c = 17.239$ (3)	$P2_12_12_1$	4	SARBOX
DL-Mannitol	$a = 9.048$ (7), $b = 4.870$ (3) $c = 18.26$ (1)	$Pna2_1$	4	DLMANT
D-Dibromomannitol	$a = 9.930$ (4), $b = 9.966$ (4) $c = 20.403$ (4)	$P2_12_12_1$	8	DEMANN
D-Mannitol (*B* form)	$a = 8.672$ (8), $b = 16.875$ (1) $c = 5.560$ (5)	$P2_12_12_1$	4	DMANTL
D-Mannitol (*K* form)	$a = 8.942$ (5), $b = 18.798$ (9) $c = 4.893$ (4)	$P2_12_12_1$	4	DMANTL01
1-Deoxy-1-nitro-L-*manno*-hexitol	$a = 5.022$ (1), $c = 61.373$ (4)	$P6_1$	6	JERHOD

* All data taken from the references given in the text unless specified.
† Taken from the Cambridge Structural Database (Allen *et al.*, 1979).
‡ Kopf, Morf, Zimmer & Köll (1991).
§ Mostad (1978).

quadrilateral homodromic hydrogen-bond cycle (group I). This cycle is built up by hydroxyl groups on an extended segment that can be found somewhere in the sugar chains of four molecules that are solely related by lattice translations. It is furthermore generalized that this segment consists of the four terminal C atoms of open-chain sugars with *arabino*, *manno*, *gluco* and *ribo* configuration and a C(6) substituted only by OH. The connectivity is O(x)—O($x + 2$)—O($x + 3$)—O($x + 1$)—O(x) with the direction of the cycle undetermined.

This packing model is purely phenomenological and by no means mechanistic. Without consideration of additional aspects, *e.g.* conditions of crystallization, the model cannot explain why, *e.g.* 1-deoxy-1-nitro-L-*manno*-hexitol, which has the same geometrical data along the chain and the terminal nitro group as the corresponding *arabino*-pentitol, does not form such a quadrilateral cycle.

Perspective

So far, there is no unequivocal way of predicting whether an acyclic sugar will crystallize in a lattice with two 5 Å axes and a homodromic arrangement or whether it will prefer other hydrogen-bond patterns. An example where the formation of a homodromic cycle may be the most important force leading to an unexpected molecular conformation is given by D-altritol, which exhibits an unusual C//O interaction in its crystal structure. Its *PAM* conformation is accomplished by a rotation of 120° around the bond C(4)—C(5), thereby resulting in the C//O interaction between O(3) and C(6). Destabilization of the extended conformation by a 1,3-*syn* interaction, however, certainly might be overcome by formation of a homodromic hydrogen-bond cycle. Kopf, Bischoff & Köll (1991) concluded from this and other 1,3-*syn* interactions that syndiaxial repulsive effects had been overestimated in the past as was suggested by Angyal, Saunders, Grainger, Le Fur & Williams, (1986). We believe that these repulsive interactions are one factor determining the crystal conformation of acyclic sugars, but that they can be overcome by an appropriate hydrogen-bonding net.

Though no mechanism for the described packing arrangement can be given so far, it might be helpful to regard an extended carbon-chain segment with four hydroxyl groups in *PAM* conformation as a separate domain that builds up part of a unit cell and generates a homodromic cycle with typical connectivity. This domain fulfils the criteria for modelling carbohydrates given by Jeffrey (1990*b*) and can be useful as a starting point in the modelling of acyclic sugars, especially if they have *arabino* or *manno* configurations and/or if the lattice constants are known. Furthermore, this hydrogen-bond cycle can be used for constructing hypothetical crystal structures of sugar derivatives which crystallize without showing this homodromic pattern. Calculating the lattice energies for both the artificial and the naturally occurring species might provide additional insight into the crystallization and packing behaviour of acyclic sugars.

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