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The crystal packing of *N*-(*n*-octyl)-D-gulonamide containing tail-to-tail sheets compared to its gluconamide diastereomer showing head-to-tail arrangement *

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ABSTRACT

N-Octylamides of diastereomeric gluconic and gulonic acids form molecular aggregates of extremely different curvature, namely helical micellar rods with a diameter of 4 nm and planar bilayers. In the crystal structure of the gulonamide compound, symmetric "tail-to-tail" bilayer sheets are observed, whereas the gluconamide derivative (whose crystal structure was determined previously) forms an unusual "head-to-tail" arrangement. These differences are unexpected because both diastereomers contain one pair each of *syn*- and *anti*-oriented hydroxyl groups in 1,3-positions of the extended aldonic acid chains. The experimental results are explained by the occurrence of hydrogen-bond patterns between hydroxyl groups, either within one crystal sheet or hydrophobic bilayer (gluconamide) or between the end groups of neighboring sheets (gulonamide).

INTRODUCTION

N-Alkylaldonamides and related derivatives having charged "head" groups provide unique properties for studying the effect of stereochemical modifications on supra-molecular structures in aqueous and organic media[1–3]. The solvophobic effect enforces the formation of spherical micellar bilayers. These soft materials rearrange to linear fibers by the cooperative formation of amide hydrogen-bond chains. The electron microscopic appearance of organized molecular bilayers ranges from planar sheets to helical rods, depending on the steric interactions between hydroxyl groups[4]. An extreme case, which is evaluated in more detail in this paper, concerns a pair of *N*-octylgulon- and glucon-amides **1** and **2**. In both open-chain aldonamides, one 1,3-*syn* oriented pair of hydroxyl groups is present.

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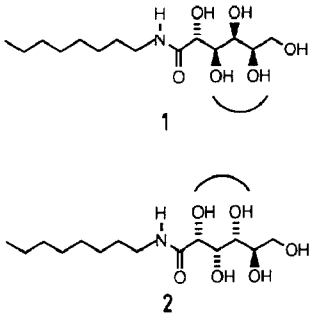
* Dedicated to Professor Dr. Hans Paulsen, Universität Hamburg, on the occasion of his 70th birthday.



Scheme 1

In the case of gulonamide **1** the outer hydroxymethine groups are in 1,3-*syn* positions. In the gluconamide **2**, the interaction occurs next to the amide group, which enforces the formation of linear fibers.

Both diastereomers are barely soluble in water at room temperature. At around 80°, amide hydrogen-bonds are broken and micellar solutions are formed. On cooling, the micelles of **2** aggregate to form helical rods of molecular bilayers. The diameter of the single fiber is ~4 nm, and the length exceeds several hundred μm. It was shown earlier that **2** then slowly crystallizes in head-to-tail (= enantiomer polar[5]) sheets[2,6]. The gulonamide **1**, on the other hand, directly forms bilayer sheets without curvature under the same conditions. In this paper we report on the crystal structure of gulonamide **1** which shows tail-to-tail sheets.

EXPERIMENTAL

Sample preparation and data collection.—The gulonamide **1** was prepared by aminolysis of D-gulonolactone by 1-aminooctane in MeOH. Very slow evaporation from water yielded a flexible plexus from which a few single crystals could be cut out. Precise lattice-constants and the intensity data for the two octands were measured at room temperature on a Stoe four-circle diffractometer with Ni-filtered Cu-K_α radiation in the ω-scan mode. Inspection of reflection profiles showed some irregularities (such as splitting and broadening) indicating moderate to poor crystal quality. In order to improve the quality of the data collection, the profiles of the intensities were saved. About 25% of them were edited before data reduction using the computer program RECOR[7]. The structure was solved by direct methods, but only the atoms of the head group moiety and the octyl chain up to C-10 were found[8] by SHELXS-86. C-11 was visible in the E-map too, but exhibited poor geometry values.

Data analysis.—Solid-state ^{2}H-NMR spectra[1] and ^{13}C-CP/MAS-NMR spectra (see later) showed that the octyl chain is disordered, generated by a remarkable mobility within the alkyl chain. This observation could be confirmed by X-ray analysis, as at least low-accuracy positions of carbon atoms for a two-site jump model of the octyl chain could be derived from rather broad maxima of

difference-Fourier maps. A similar behavior of an alkyl chain has been observed at room temperature with hexyl 1-thio-β-D-xylopyranoside, where the hexyl chain is, in fact, totally invisible in the difference-Fourier map[9]. The model that best fits the difference map in the case of **1** shows two positions for C-8 and C-9, whereas the positions of the other atoms of the octyl chain remain unaltered. The positional parameters of the atoms C-81 to C-14 could not be refined to convergence with reasonable geometry, so that they had to be refined through several cycles with a damping factor without converging to obtain at least an estimate of their errors. Consequently, their U-values were only refined isotropically. No attempt was made under these circumstances to refine the population ratio of the octyl chain, which was held fixed at 0.50 in all disordered cases. The resulting bond-lengths and angles show comparatively large differences from the standard values of the alkyl-chain region. We do not regard these differences to be significant because of the high standard deviations. The atoms of the gulonamide moiety and C-7, however, could be refined anisotropically to reasonable geometry and U-values.

Data refinement.—There were no hydrogen atoms located after the anisotropic refinement of the gulonamide moiety, but hydrogen-atom positions were calculated for the carbon atoms of the sugar moiety, the nitrogen atom of the amide bond and the disordered octyl chain. They were given isotropic thermal parameters by adding ~ 10% to the values for their corresponding heavy atoms. No hydrogens were assigned to the hydroxyl groups.

The final refinement resulted in a weighted *R*-value of 14.8% (unweighted *R*-value 16.7%). This poor value must primarily be attributable to the extreme mobility of the octyl chain, which makes it impossible to derive exactly defined atomic positions, and is not simply a consequence of poor crystal quality, the

TABLE I

Crystal and refinement data for **1** [a]

Formula	$C_{14}H_{29}NO_6$
Space group	C2
Lattice constants (pm)	$a = 969.2(8)$
	$b = 507.7(3)$
	$c = 3457(3)$
	$\beta = 96.70(7)°$
Cell volume (pm^3)	1.6895×10^9
Crystal size (mm)	$1.2 \times 0.3 \times 0.07$
ρ_x (g/cm^3)	1.208
μ (Cu-K_α, cm^{-1})	7.84
Reflections	1445
unobserved ($F < 2\sigma$)	128
R_F	16.7%
wR_F	14.8%
S	13.26
Function minimized	$\Sigma[\sigma^{-2}(F_o)(\lvert F_o \rvert - \lvert F_c \rvert)^2]$

[a] Numbers in parentheses are ESD values.

TABLE II

Atomic parameters and U_{eq}- and U-values for **1** [a]

Atom	x	y	z	U_{eq}
C-1	0.802(2)	0.7853(–)	0.2979(6)	6.4(7)
O-1	0.845(1)	0.571(4)	0.2895(4)	9.5(6)
C-2	0.697(2)	0.800(4)	0.3294(5)	5.8(6)
O-2	0.644(1)	1.056(4)	0.3305(4)	8.2(5)
C-3	0.762(1)	0.716(4)	0.3692(6)	5.1(6)
O-3	0.812(1)	0.454(4)	0.3681(3)	8.1(6)
C-4	0.668(1)	0.763(4)	0.3984(5)	5.1(5)
O-4	0.5416(9)	0.627(3)	0.3869(3)	5.8(4)
C-5	0.733(1)	0.638(4)	0.4390(5)	6.2(7)
O-5	0.6335(8)	0.705(3)	0.4677(3)	7.1(5)
C-6	0.868(2)	0.752(5)	0.4557(5)	6.6(8)
O-6	0.869(1)	1.016(3)	0.4585(4)	6.9(5)
N	0.830(1)	1.007(4)	0.2823(5)	7.0(6)
C-7	0.923(2)	0.995(5)	0.2515(5)	7.4(7)
C-81	0.848(8)	1.13(2)	0.213(2)	8(2)
C-91	0.735(6)	0.99(1)	0.194(2)	5(1)
C-8	0.889(6)	0.96(1)	0.213(2)	5(2)
C-9	0.769(9)	1.13(2)	0.199(2)	9(2)
C-10	0.698(6)	1.02(2)	0.153(1)	15(2)
C-11	0.564(8)	1.05(2)	0.138(2)	19(3)
C-12	0.507(7)	0.99(2)	0.094(2)	18(2)
C-13	0.375(8)	1.05(3)	0.077(3)	27(4)
C-14	0.312(8)	1.02(2)	0.038(2)	23(3)

[a] Numbers in parentheses are ESD values.

influence of which on intensity accuracy is assumed to have been diminished by reflection-profile editing. Therefore, the parameters for C-81 to C-14 should be regarded with some reservation, but the head group exhibits reasonable geometry as compared with other acyclic-sugar derivatives. Repetition of the analysis with a second crystal resulted in the same data, within experimental error. An attempt to collect intensity data at low temperatures failed as the only remaining crystal cracked upon cooling.

Crystal-packing scheme of **1** *and the conformation of its sugar moiety.*—These questions could be answered unambiguously. Moreover, a structure can be presented wherein the X-ray single-crystal analysis and solid-state NMR spectra give concordant information on the solid-state behavior of **1**.

Table I displays the crystal and refinement data for **1**, the atomic parameters are listed in Table II * and the relevant bond lengths and torsion angles are given in Table III. The hydrogen-bond geometry with the amide group involved and

* A complete atom list, including the hydrogen atom and displacement parameters, together with the list of observed and calculated structure-factors and the list of bond angles for **1** can be obtained on request from Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/500/*Carbohydr. Res.*, 230 (1992) 31–40.

TABLE III

Torsion angles of the carbohydrate moiety in **1** [a]

Sequence	Angle (degrees)
O-1–C-1–C-2–C-3	66(2)
C-1–C-2–C-3–C-4	173(1)
C-2–C-3–C-4–C-5	173(2)
C-3–C-4–C-5–C-6	62(2)
C-4–C-5–C-6–O-6	52(2)
O-1–C-1–C-2–O-2	−171(1)
O-2–C-2–C-3–O-3	178(1)
O-3–C-3–C-4–O-4	−70(2)
O-4–C-4–C-5–O-5	−65(2)
O-5–C-5–C-6–O-6	−64(2)

Bond lengths and torsion angles of the octylchain in **1** [a,b]

C-7–C-8	134(7)	C-7–C-81	159(8)
C-8–C-9	149(10)	C-81–C-91	140(10)
C-9–C-10	172(10)	C-91–C-10	139(8)
C-10–C-11	136(9)	C-11–C-12	158(10)
C-12–C-13	140(10)	C-13–C-14	140(10)

Sequence	Angle (degrees)
C-7–C-8–C-9–C-10	−165(5)
C-8–C-9–C-10–C-11	153(9)
C-9–C-10–C-11–C-12	172(8)
C-10–C-11–C-12–C-13	−170(11)
C-11–C-12–C-13–C-14	176(12)
C-7–C-81–C-91–C-10	−153(7)
C-81–C-91–C-10–C-11	−136(9)
C-91–C-10–C-11–C-12	−156(9)

[a] ESD values in parentheses. [b] Bond lengths in pm.

TABLE IV

Summary of hydrogen-bonding data in **1** [a,b]

At the amide nitrogen

X–H ··· Y	X ··· Y	X–H	H ··· Y	X–H ··· Y	Symmetry operation for Y
N–H-N ··· O-1	287(3)	101(2)	205(2)	136(1)	$x, 1+y, z$
N–H-N ··· O-2	260(2)	101(2)	219(1)	102(1)	x, y, z
O-2 ··· O-1	364(2)	O-2 ··· H-N ··· O-1		118(1)	
			sum	359(1)	

Oxygen–oxygen distances [a]			Symmetry operation for atom 2
Atom 1	Atom 2	D [b]	
O-5	O-6	272(2)	$-1/2+x, -1/2+y, z$
O-5	O-6	273(2)	$3/2-x, -1/2+y, 1-z$
O-3	O-4	279(2)	$1/2+x, -1/2+y, z$
O-5	O-6	282(2)	x, y, z
O-2	O-3	282(2)	$x, 1+y, z$
O-4	O-5	286(2)	x, y, z
O-2	O-1	308(2)	$-1/2+x, 1/2+y, z$

[a] Distances in pm. [b] ESD values in parentheses.

oxygen–oxygen distances indicating reasonable hydrogen bonds are shown in Table IV.

RESULTS AND DISCUSSION

The molecular geometry of gulonamide **1** is displayed in Fig. 1. The head-group region exhibits an AAP-"sickle" conformation, generated by the 1,3-*syn* interaction between the hydroxyl groups at C-3, and C-5. The torsion angle C-3–C-4–C-5–C-6 is 60°. This gauche conformation corresponds to the expected molecular structure of open-chain alditols having such a pair of *syn*-diaxially oriented hydroxy groups[11].

A second bend occurs at the amide group, where the angle N–C-7–C-8–C-9 is +45°. This "S-like" conformation of the polar region leads to a relatively large lateral space for the oligomethylene chain, which therefore might appear in different orientations (Fig. 1).

Solid-state ^{2}H-NMR spectroscopy of **1** also reflected this extraordinary mobility, whereas the spectra of **2**, containing a linear head-group conformation in the crystalline state, showed the Pake pattern of solid material[1].

Circumstantial evidence for an all-*trans* conformation of the oligomethylene chain in gulonamide **1** comes from a comparison of solid-state ^{13}C-CP/MAS-NMR spectra. The octyl chains of both the gulonamide **1** and gluconamide **2** produce exactly the same pattern of eight signals for the methylene and methyl groups. This is not expected for chains of different conformations, as chemical-shift differences resulting from conformational isomerism may be as large[12] as 8–12 ppm.

The arrangement of the molecules in the crystal is parallel tail-to-tail, without any interdigitation (Fig. 3). The amide hydrogen is involved in a bifurcated three-center bond, intramolecular to O-2 and intermolecular to O-1 with hydrogen–oxygen distances of 219 and 205 pm respectively. The corresponding nitrogen–oxygen distances are 260 and 287 pm. Although no hydrogen atoms of the hydroxyl groups could be localized, the intermolecular oxygen–oxygen distances between 272 and 308 pm suggest strong bonds (Table IV).

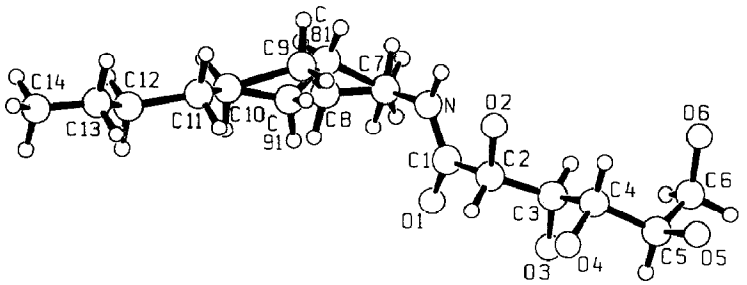


Fig. 1. Molecular conformation of gulonamide **1**. Both possible positions of the polymethylene chain are shown (SCHAKAL-88b[10]).

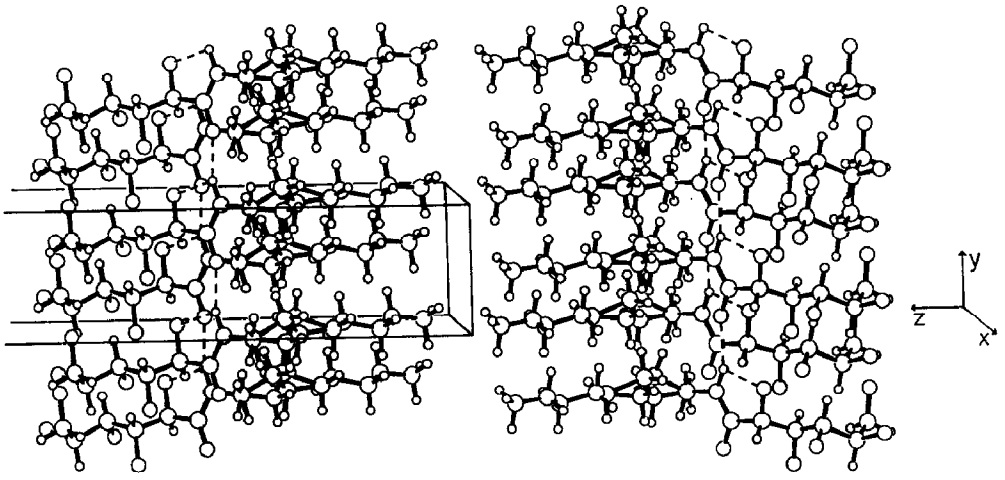


Fig. 2. Molecular packing of 1 shows the usual tail-to-tail orientation of amphiphiles. Atoms H, C, N, O are indicated with increasing radii and hydrogen bonds by dotted lines.

An important feature comes from the *gauche* conformation at the outer hydroxymethine and hydroxymethylene groups. This bend produces a *polar* edge on the crystalline sheets and allows the formation of hydrogen bonds between head groups of two adjacent crystal sheets. As shown in Fig. 3, the oxygen atoms O-5 and O-6 are involved in inter- and intra-layer bonds between neighboring molecules. Adjacent sheets are thus connected by cycles of hydrogen bonds in a "zip"-like highly cooperative manner, resulting in the usual tail-to-tail arrangement of amphiphiles. Very similar behavior has been observed with related monoglycerides of fatty acids[13–16]; thus the 1-monoglyceride of 11-bromoundecanoic acid shows the same cycle as described here[13].

The crystal structure differs significantly from that of the diastereomeric gluconamides. All homologues having heptyl[17], octyl[6], decyl[17], and undecyl[18] chains produce head-to-tail arrangements of the crystal sheets. The molecules are oriented parallel, with the all-*trans* conformation of both the aliphatic and the gluconic moieties. The hydroxyl groups are involved in a quadrilateral ("homodromic"[19]) cycle of hydrogen bonds within an individual sheet. The cycle leads to a "backward" orientation of the terminal hydroxyl group, thus producing an *apolar* edge in the head group and the crystal sheet, respectively. Similar arrangements of crystal sheets, as well as of the terminal hydroxyl groups, have been found in *N*-(2-chloroethyl)-[20] and *N*-benzyl-[21] gluconamide.

A common feature of all crystal structures described here so far is the existence of intermolecular amide hydrogen bonds. If these bonds are absent, as in the 1-deoxy-(*N*-methylalkanamido)glucitols having nonyl[22] or undecyl[23] methylene chains, the head-to-tail arrangement is also found. Because of the distortion of the glucitols by the *N*-methyl group, the inner bend of the gluconic moiety appears, produced by the 1,3-*syn* interaction of the hydroxyl groups at C-2 and C-4. If bulky

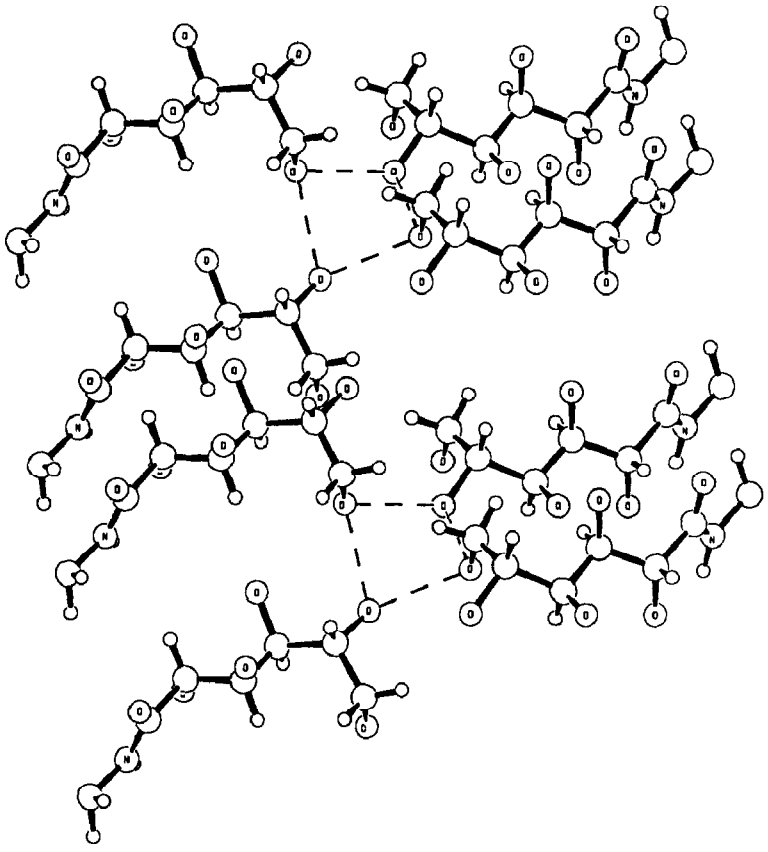


Fig. 3. Hydrogen-bonding scheme of **1**. For clarity only the polar moiety of the amphiphile is shown. The molecules are connected by hydrogen-bond cycles over the gap between two adjacent crystal sheets. Note the polar edge on the sheet of **1**.

hydrophobic tails such as *N*-cyclohexyl[24], *N*-isopropyl, or *N*,*N*-diethyl[25] hinder crystal packing, compensation by antiparallel head-to-tail arrangements will occur. Despite such specific differences, all compounds show strong intralayer hydrogen-bond schemes, including the backward orientation of the terminal hydroxyl group. The interaction between the homodromic cycle and molecular orientation within the crystals was qualitatively discussed recently by Jeffrey[26].

We demonstrated a close relationship between intralayer hydrogen bonding and glyconamide stereochemistry. For this purpose we chose as reference the crystal structure of the D-gluconamide, which contains the homodromic hydrogen-bond cycle. In this structure, short hydrogen-bonds ($\leqslant 200$ pm) run smoothly from one plane to another. If one assumes the same molecular arrangement in racemic D,L-gluconamide, the corresponding hydrogen atom of D-gluconamide finds no partner in the L-gluconamide molecule (Fig. 4b). A similar situation is found in D-gulonamide layers. Neither the hydroxyl-group pair at C-5 and C-6 (as indicated in Fig. 4c), nor any other hydroxyl-group pair can form a hydrogen-bond cycle.

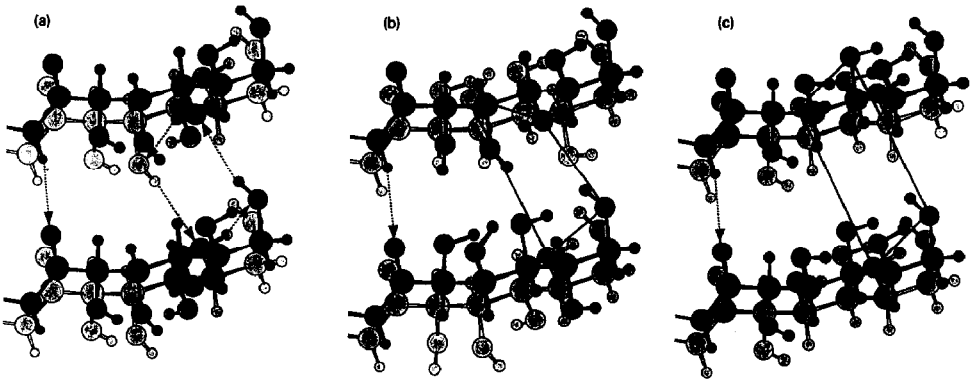


Fig. 4. The "homodromic" hydrogen-bond cycle of D-gluconamide **2** between two neighboring layers within one crystal sheet (a)[6]. In the same molecular arrangement, racemic D,L-gluconamide (b) and D-gulonamide (c) cannot form a corresponding hydrogen-bond pattern (as shown by the fictional cycle). Thus the rearrangement to tail-to-tail is favored. For orientation, the amide hydrogen bond is identified by an arrow.

Inversion of spatial orientation of the hydroxyl groups at C-3 and C-4 thus also destroys the homodromic cycle.

The forces between the head groups of amphiphilic molecules are of great importance for the aggregation behavior. It has long been known that esterification of fatty acids enforces a rearrangement from the tail-to-tail to the head-to-tail orientation, because the alcohol chains weaken the interaction between polar groups[27,28]. The extraordinary head-to-tail arrangement of crystalline sheets of gluconamide is thus triggered by a stable homodromic hydrogen-bond cycle, which causes the surface of the micellar bilayer to be relatively hydrophobic. Reorientation of the amphiphiles from tail-to-tail to head-to-tail becomes facile and allows identical positioning of all chiral centers in the crystal. Enantiomeric polar crystals are thus favored. In both the gulonamide **1** and racemic mixtures of D- and L-gluconamides, the homodromic hydrogen-bond cycles cannot be formed and the bilayer surfaces become more hydrophilic. Interbilayer interactions become dominant and the chiral centers are positioned in "mirror-image" or "pseudo-mirror" image positions.

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