Conformational Effects of 1,3-*syn*-Diaxial Repulsion and 1,2-*gauche* Attraction Between Hydroxy Groups in Monomolecular *N*-Octyl-D-hexonamide Solutions. A ^{13}C and ^{1}H NMR Spectroscopic Study

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Homo- and hetero-nuclear NMR-techniques were used to assign signals and coupling constants to vicinal CH and CH–OH protons in *N*-octyl-D-hexonamides **1–5** (galacton, mannon, glucon, talon and gulon) dissolved in DMSO. Analysis of the data showed (*i*) quite uniform conformations for all hexonamides and a particular rigidity about the central C-3–C-4 bond, (*ii*) a dominating attractive *gauche*-interaction between neighbouring hydroxy groups, (*iii*) strong repulsion between *syn*-diaxial 1,3-hydroxy groups and (*iv*) no internal hydrogen bonds. All conformations found experimentally in solution result from the interaction of both effects, but neither the attractive nor the repulsive intramolecular interactions are of importance in supramolecular assemblies or crystals.

N-Octyl-D-hexonamides dissolve in hot water to form spherical micelles at a cmc of 2×10^{-3} mol dm^{-3}. Upon cooling the secondary amide groups form hydrogen bond chains and the spherical micelles rearrange and aggregate to form long micellar fibres of bimolecular thickness. Depending on the stereochemistry of the carbohydrate head groups micellar quadruple helices, twisted ribbons, vesicular tubules and various other shapes are observed. It is also found that pure enantiomers usually assemble to form fibres, whereas the corresponding racemates precipitate as platelets without any curvature.[1–7] Since in these uniform fibres the effects of hydrophobicity, hydrogen bonding and stereochemistry on molecular arrangements can be analysed directly by the electron microscopy and solid state NMR spectroscopy, we now report investigations into the hexonamide conformations in solution, fibrous aggregates and 3-D crystals in detail.

Herein we evaluate the *N*-octyl-D-hexonamides **1–5** in DMSO solution. Their stereochemistry in the all-*anti* conformation is depicted in Fig. 1. The hexonamides can be divided into three groups: (I) with no 1,3-*syn*-diaxial arrangement (O//O) of oxygen atoms (galacton-, mannon-amide); (II) with one O//O position between O-2 and O-4 (glucon-, talon-amide); or (III) between O-3 and O-5 (gulonamide). Of all the interactions in such acyclic polyols, the O//O-arrangements are thought to be the most destabilizing.[8–11] They should determine the relative populations of different conformers in solution.[12] The galacton- and mannon-amides **1** and **2** with no such O//O-arrangement should preferentially exist as planar zigzag conformers, whereas the glucon-, talon-, and gulon diastereoisomers **3–5** should prefer sickle conformations to avoid the O//O interaction of the planar conformers. This valid argument cannot explain, however, by any means, the enormous differences in solubilities and supramolecular structures between **1** and **2** and between **3**, **4** and **5**, which are observed. Furthermore, recent studies have given a good few examples of molecular structures, where linear conformations with avoidable O//O or C//O interactions occur.[13–16] On the other hand, it was also found that molecular dynamic calculations are notoriously unreliable. For example, they produce very similar conformational energies for most different molecular shapes of glucitol and octyl gluconamide.[5,17] In order to explain the conformations of **1–4** in DMSO solution, which were found to be quite uniform for a given hexonamide, we shall only assume an attractive *gauche* interaction between vicinal oxygen atoms.[18–23] All conformations then could be explained perfectly by the interaction between repulsive O//O position and this attractive *gauche* effect. We shall also demonstrate that intramolecular hydrogen bonds do not occur. Such interactions have, for example, been implied by Eschenmoser in a discussion of allose conformations.[24]

Experimental

Synthesis of N-(1-*Octyl*)-D-*hexonamides*.—Aminolyses of the hexonic acid 1,4- or 1,5-lactones (Sigma) were performed by heating with an equimolar amount of 1-aminooctane (Fluka) in methanol. The products were crystallized from methanol and characterized by IR and NMR spectroscopy and mass spectra, as well as elemental analyses.[1–3]

Spectral data. Each sample contained 80 mg of the hexonamide crystals dissolved in 0.5 cm^3 [$^2H_6$]DMSO. NMR spectra were recorded at 500 MHz proton resonance and 125 MHz ^{13}C-resonance, respectively (Bruker AMX 500). Digital resolutions of the spectra amounted to 0.13 Hz/point (^1H) and 0.35 Hz/point (^{13}C). A line broadening of 1.2 Hz was applied. The spectra were referenced to tetramethylsilane and DMSO (δ 39.5) as internal standards. The temperature was maintained at 25 °C using a variable temperature unit (Bruker B-VT 2000).

^1H NMR Peak assignment was performed by means of homonuclear decoupling. Low decoupling power (30 W) was chosen in order to avoid irradiation of neighbouring nuclei. NOE experiments were performed using a selective presaturation scheme with irradiation at different frequencies within one multiplet (Bruker standard pulse program noemul). Total mixing time amounted to 6.4 s. During NOE measurements the sample was not spun to minimize artefacts originating from probe rotation. 2D ^{13}C–^1H Heteronuclear chemical shift correlation experiments were employed for the assignment of ^{13}C resonances, using a pulse sequence of Bax and Morris (Bruker pulse program hxco). Broad band decoupling during the acquisition period was achieved by means of WALTZ-16 composite pulse decoupling. 2048 Data points were acquired in the t_2 domain with a dwelltime of 50 μs (^{13}C) and 1024 FIDs in the t_1 domain with a time increment of 200 μs (^1H). This results, after sine multiplication and zero-filling, in t_1 in digital resolutions of 1.22 Hz/point (^1H) and 9.76 Hz/point (^{13}C).

Simulations of spectra. The experimental data were fitted by spectral simulation in order to improve on the accuracy of the chemical shifts and coupling constants. Limitation of the applied RACCOON simulation program to seven nuclei was

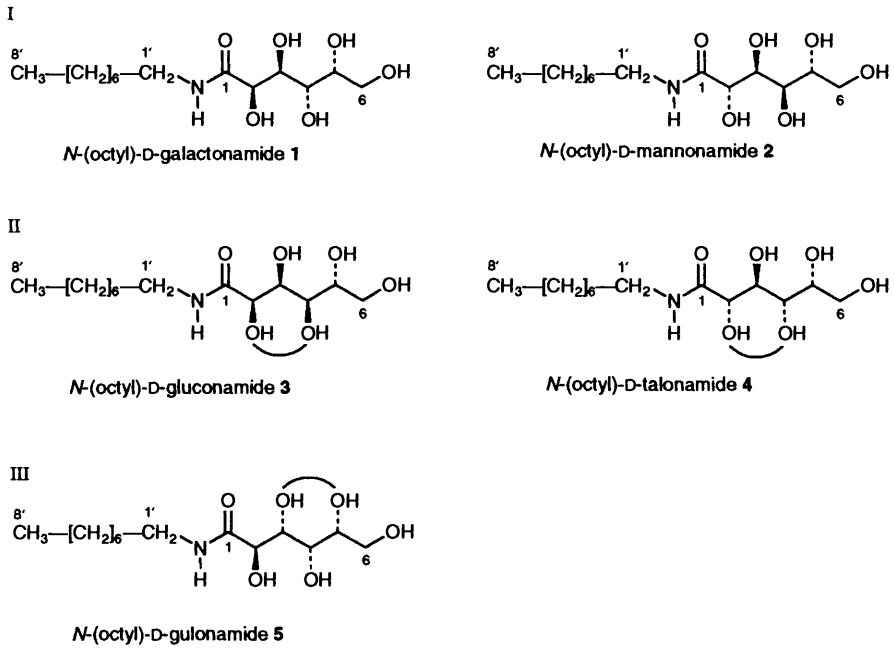

Fig. 1 Schematic representation of the *N*-(1-octyl)-D-hexonamides **1–5** with all-*anti* conformation and 1,3-*syn*-diaxial orientation of oxygen atoms

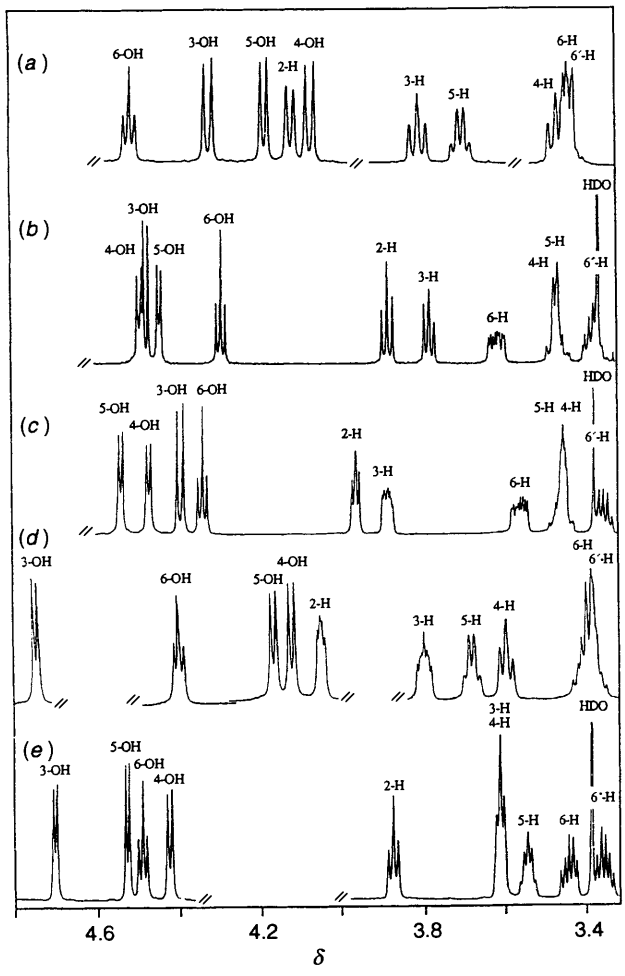

Fig. 2 ^{1}H NMR Spectra and peak assignments of the head group signals of hexonamides **1–5** ([$^2H_6$] DMSO; TMS; 500 MHz)

circumvented by simulating two sub-spectra. Hydrogen atoms at C-2, C-3 and C-4 as well as 5-H were considered in one group, hydrogen atoms at C-4 to C-6 in the other.

Table 1 ^{1}H NMR Chemical shifts (ppm) down from tetramethylsilane and vicinal $^3J_{H,OH}$ coupling constants (Hz) of the octyl hexonamides **1–5** in [$^2H_6$]DMSO solution at 500 MHz

	1	2	3	4	5
2-H	4.14	3.86	3.98	4.08	3.89
3-H	3.80	3.76	3.90	3.79	3.62
4-H	3.45	3.45	3.47	3.57	3.62
5-H	3.70	3.44	3.48	3.66	3.54
6-H	3.42	3.60	3.58	3.38	3.43
6'-H	3.41	3.36	3.38	3.36	3.34
2-OH	5.07	5.46	5.34	5.49	5.46
3-OH	4.30	4.46	4.40	4.78	4.66
4-OH	4.10	4.48	4.47	4.15	4.35
5-OH	4.19	4.43	4.54	4.20	4.47
6-OH	4.44	4.28	4.34	4.41	4.43
$J_{2,OH}$	7.10	6.70	5.00	5.60	6.30
$J_{3,OH}$	8.00	5.70	7.00	5.50	4.70
$J_{4,OH}$	7.80	6.20	5.00	7.10	6.00
$J_{5,OH}$	6.50	4.80	5.00	6.80	4.80
$J_{6,OH}$	5.70	5.70	5.70	5.60	5.60
$J_{6',OH}$	5.70	5.70	5.70	5.60	5.60

Results

Unequivocal ^{1}H NMR peak assignments of the *N*-(1-octyl)-D-hexonamides **1–5** in DMSO solution were carried out by homonuclear spin decoupling experiments at 500 MHz. The resulting head group peak patterns are shown in Fig. 2. The head group conformations were then determined by an evaluation of vicinal $^3J_{H,H}$ and $^3J_{H,OH}$ coupling constants. They were obtained either directly from the spectra or by the RACCOON spectra simulation program.[25] Chemical shifts and $^3J_{H,OH}$ coupling constants are given in Table 1. The observed $^3J_{H,H}$ values are listed in Table 2, together with calculated coupling constants for *gauche* and *anti* oriented, as well as for freely rotating vicinal methine hydrogens, obtained by the ALTONA program using modified Karplus equations.[26,27]

The ^{13}C NMR signals were assigned by two-dimensional heteronuclear ^{13}C–^{1}H-shift correlation experiments.[17,28,29] The chemical shifts of all hexonamide signals are reproduced in Table 3.

Comparisons of observed and calculated $^3J_{H,H}$ coupling constants (Table 2) yield *gauche*, *anti* and *gauche* orientations

Table 2 Observed and calculated $^3J_{H,H}$ coupling constants (Hz) and estimated *anti*-percentage P_a (%) of vicinal hydrogens of the hexonamides **1–5**

Compound	Obs.	60°	180°	−60°	Free rot.	P_a
1 $J_{2,3}$	1.20	0.54	9.88	4.04	4.82	
$J_{3,4}$	8.90	2.28	9.72	2.28	4.76	
$J_{4,5}$	1.60	4.02	9.57	0.54	4.71	
$J_{5,6}$	6.20	0.90	10.68	5.01	5.53	
$J_{5,6'}$	6.70	3.07	10.68	2.84	5.53	
2 $J_{2,3}$	6.70	0.54	9.88	4.04	4.82	
$J_{3,4}$	0.50[a]	4.02	9.57	0.54	4.71	
$J_{4,5}$	8.50[a]	2.27	9.57	2.29	4.71	
$J_{5,6}$	2.50	0.90	10.68	5.01	5.53	
$J_{5,6'}$	5.00	3.07	10.68	2.84	5.53	
3 $J_{2,3}$	4.50	0.54	9.88	4.04	4.82	30
$J_{3,4}$	3.40[a]	4.02	9.57	0.54	4.71	0
$J_{4,5}$	3.00[a]	2.27	9.57	2.29	4.71	10
$J_{5,6}$	2.50	0.90	10.68	5.01	5.53	20[b]
$J_{5,6'}$	5.00[a]	3.07	10.68	2.84	5.53	
4 $J_{2,3}$	3.60[a]	2.29	9.88	2.29	4.82	20
$J_{3,4}$	8.60[a]	2.28	9.72	2.28	4.76	85
$J_{4,5}$	1.40[a]	4.02	9.57	0.54	4.71	0
$J_{5,6}$	6.20	0.90	10.68	5.01	5.53	85[b]
$J_{5,6'}$	6.30	3.07	10.68	2.84	5.53	
5 $J_{2,3}$	6.30	2.29	9.88	2.29	4.82	50
$J_{3,4}$	2.40[a]	0.54	9.72	4.03	4.76	0
$J_{4,5}$	5.20[a]	4.02	9.57	0.54	4.71	40
$J_{5,6}$	4.60	0.90	10.68	5.01	5.53	60[b]
$J_{5,6'}$	5.70	3.07	10.68	2.84	5.53	

[a] Obtained by the RACCOON spectra simulation program. [b] *anti* Orientations between 5-H and 6-H/6′-H are combined.

Table 3 ^{13}C NMR Chemical shifts (ppm) of the hexonamides **1–5** in [$^2H_6$] DMSO solution

	1	**2**	**3**	**4**	**5**
C-1	173.17	173.52	172.30	172.29	173.07
C-2	71.02	71.94	73.71	73.02	71.83
C-3	70.83	70.53	70.16	72.93	72.76
C-4	69.23	70.32	72.48	69.92	69.51
C-5	69.86	70.92	71.52	70.33	73.14
C-6	63.25	63.77	63.43	62.93	62.52
C-1′	38.39	38.34	38.31	38.20	38.35
C-2′	29.36	29.11	29.24	29.14	29.09
C-3′[a]	26.48	26.40	26.45	26.43	26.41
C-4′[a]	28.79	28.73	28.77	28.72	28.72
C-5′[a]	28.89	28.80	28.86	28.80	28.79
C-6′	31.37	31.32	31.35	31.30	31.31
C-7′	22.20	22.16	22.19	22.14	22.15
C-8′	14.02	14.02	14.02	14.00	13.97

[a] Assigned by analogy to Bull *et al.*[46]

between the vicinal hydrogen atoms 2-H/3-H, 3-H/4-H and 4-H/5-H of galactonamide **1**, corresponding to the linear head group conformation (Fig. 3). The constants for 3-H/4-H and 4-H/5-H couplings in mannonamide **2** are also in agreement with the *gauche* and *anti* positions of the linear conformation (Fig. 3). The expected *anti* orientation between 2-H and 3-H, however, is realized to only about 60%. Some bent conformers are clearly present in solution. Mannonamide **2** is thus more flexible than galactonamide **1**, which also explains the much better solubility and lower melting point.[3] The terminal hydroxymethyl groups of **1** and **2** are freely rotating. The planar head group conformations of both amides (Fig. 4) correspond to those of galactitol and mannitol[19] as well as galactonic and mannonic acid.[30]

Because of the deviations between observed and calculated coupling constants for gluconamide **3** (Table 2), we estimated the percentage of *anti* positioned hydrogens P_a around each C–C bond[17,31] using eqn. (1).

$$P_a = \frac{J_{obs} - (J_{g+} + J_{g-})/2}{J_a - (J_{g+} + J_{g-})/2} \quad (1)$$

The result (Table 2) shows that the hydrogen atoms 3-H/4-H and 4-H/5-H are to about 100% and 90% in a *gauche* orientation. The latter is in contrast to the extended conformation of **3** and points to a sickle conformation. Clockwise or counterclockwise rotation of C-5 around the C-4–C-5 axis by 120° leads to the $_4G^-$ (not shown) or $_4G^+$ (Figs. 3, 4) sickle conformations in the notation of Flory.[32] The remaining fraction of *anti*-hydrogens at C-2/C-3 and C-5/C-6 is close to the value of 33% for free rotation. The 1,3-*syn* repulsion between O-2 and O-4 thus only induces rotation but no $_2G^-$ sickle conformation as observed in glucitol.[19]

Both $_4G$ sickle conformations of **3** should also cause up-field shifts of the C-3 and C-6 signals ('γ-*gauche* effect')[33,34] as compared to the linear mannonamide **2** (Fig. 3). This effect is indeed reflected in the ^{13}C NMR chemical shifts (Table 3). It remains to be decided which of the conformations occurs preferentially in DMSO solution. A first hint comes from a comparison with the spectrum of glucitol, where the chemical shift of C-3 (δ 68.8)[10] is dominated by shielding *gauche* interactions with O-1 and O-5. This situation is similar to the $_4G^-$ sickle with *gauche* orientations between C-3 and O-5/C-6, whereas in the $_4G^+$ sickle C-3 and O-5 are *anti* oriented. The downfield position measured for the C-3 signal of gluconamide **3** (δ 70.16) thus points to the $_4G^+$ conformation. Supporting evidence comes from NOE experiments:[35] a comparison of nuclear distances extracted from ball and stick models reveal that the 5-OH proton is much closer to 4-H and 4-OH protons in the $_4G^+$ conformation (0.22 nm and 0.26 nm) than in the $_4G^-$ conformation (0.40 nm for both). Similar differences are observed for 3-H: the distance to 5-H is 0.29 nm in the $_4G^+$ sickle and 0.41 nm in the $_4G^-$ case and the distances to the methylene hydrogen atoms 6-H/6′-H amount to 0.31/0.45 nm ($_4G^+$) and 0.41/0.26 nm ($_4G^-$) respectively. Irradiation of the 5-OH proton intensifies the overlapping signals of the protons on C-4 and C-5 by 6.1%, with a somewhat larger effect on 4-H. The latter proton should therefore be closer to 5-OH. Irradiation of 3-H intensifies the signals of 4-H, 5-H and 3-OH (Fig. 5). There is no evidence for a significant intensity gain of the methylene signals, as would be expected for the $_4G^-$ sickle. The smaller intensity changes of all other signals are due to chemical exchange. The NOE experiments thus confirm the conclusions discussed above: the conformer of gluconamide **3** in DMSO which produces the NMR solution spectrum is the $_4G^+$ sickle depicted in Fig. 4.

The observed coupling constants for 3-H/4-H and 4-H/5-H of talonamide **4** agree with the *anti* and *gauche* orientations of the planar conformation. The $^3J_{H,H}$ value for 2-H/3-H, however, points to a *gauche*-bent, resulting in a $_2G^-$ or $_2G^+$ (Fig. 4) sickle conformation. In both cases the 1,3-*syn* repulsion between O-2 and O-4 is removed. In the $_2G^-$ sickle, however, an equally unfavourable C-1//O-4 interaction occurs. Supporting evidence for the remaining $_2G^+$ sickle may be drawn from a comparison with galactonamide **1**, which contains the same shielding H//O orientation[11,19] between 2-H and O-4 (see dotted arrows in Fig. 4). This results in similar chemical shift differences for C-2 and C-3 signals of **1** and **4** ($\Delta\delta$ 0.22 and 0.10), although the overall stereochemistry of talon- and galacton-amides is quite different (Fig. 1).

For gulonamide **5** neither the comparison of observed and

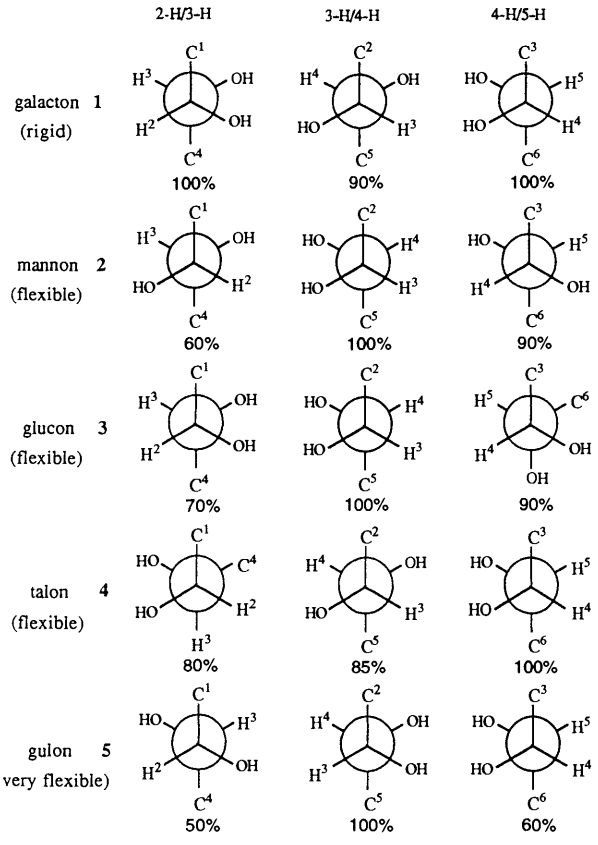

Fig. 3 Newman projections of the chiral carbon atoms in the determined conformations of hexonamides **1**–**5** in DMSO solution. The percentage numbers indicate the fraction of the given orientations between vicinal hydrogen atoms.

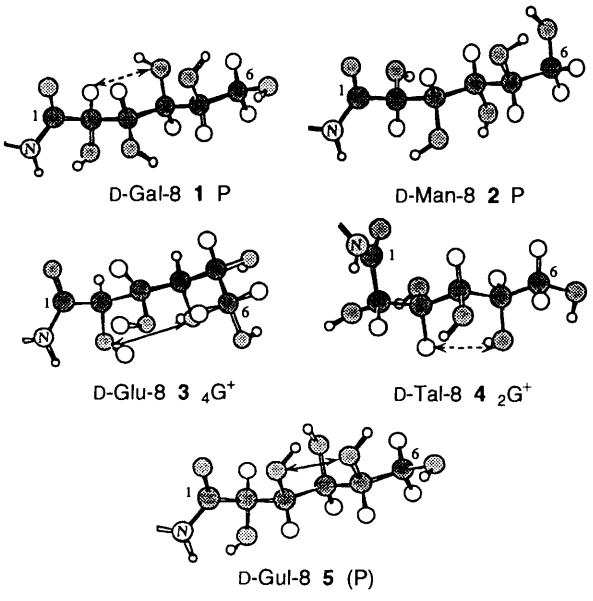

Fig. 4 Ball and stick models of the experimental head group conformations of hexonamides **1**–**5** in DMSO solution. The arrows indicate O//O and the dotted arrows H//O interactions.

calculated coupling constants (Table 2) nor the *anti*-percentage P_a of vicinal hydrogens yield a major conformation in DMSO solution. There seems only to exist one favoured *gauche* orientation, namely between 3-H and 4-H (Fig. 3). Such mixture of conformers, which is not found in the other hexonamides **1**–**4**, should be responsible for its inability to form organized supramolecular structures in hydrating environments.

We also investigated the possibility, that preferred con-

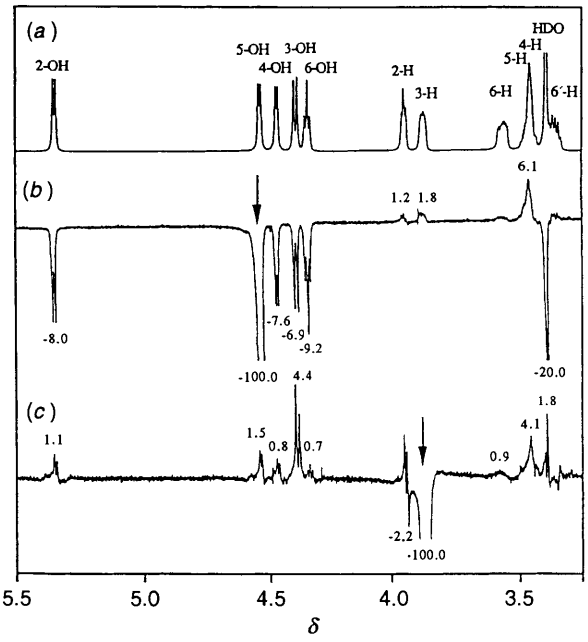

Fig. 5 (*a*) ^{1}H NMR Spectrum of the gluconamide **3** head group found in [$^2H_6$]DMSO; (*b*) and (*c*) difference spectra between NOE and ^{1}H spectra. The numbers give relative intensity changes (%).

formations of the hexonamides in DMSO solution are stabilized by intramolecular hydrogen bonds. Inter- and intra-molecular hydrogen bonds are distinguishable by temperature dependent measurements of chemical shifts. The NMR signals of protons participating in intermolecular bonds shift up-field with increasing temperature, whereas the chemical shifts of protons involved in intramolecular hydrogen bonds are temperature independent, limiting temperature coefficients $d\delta/dT$ to those of aliphatic hydrogen atoms.[36–38] We determined the chemical shifts of the hydroxy protons in the temperature range from 22 to 90 °C for gluconamide **3** (Fig. 6). All proton signals shifted linearly to higher field compared to the methine hydrogen peaks, indicating intermolecular hydrogen bonds only. The S=O group of DMSO acts as a strong acceptor of hydrogen bonds and therefore hinders the formation of inter- and intramolecular bonds between solute molecules.[39–41]

Discussion

The first important result of this study is the experimental demonstration that the open chain hexonamides **1**–**4** show highly favourable, in most positions even fixed conformations, in monomolecular DMSO solution. This is the case although no stabilizing intramolecular hydrogen bonds occur. This rigidity comes as a surprise, since it is not reflected in molecular dynamic calculations, nor is there any obvious barrier to rotation of the C–C bonds or repulsive steric interaction which would distinguish **1** and **2**, or **3**, **4** and **5**. The second result consists of a preferred *gauche* orientation of adjacent hydroxy groups (see Fig. 3), which has so far only been found in small vicinal diols[20–23] and was discussed for allitol and iditol.[19] The basic requirement of the attractive *gauche* effect of oxygen atoms is an *anti*-parallel orientation between a C–O and an adjacent C–H bond, as optimally realized within the xylo-configuration.[18–20] In solution the planar conformation of xylitol is thus much more stable than in ribitol, although in both molecules O//O interactions occur.[20,31] The unexpected and most interesting conformation is the $_4G^+$ sickle of gluconamide **3**, where the O-2//O-4 interaction is preserved. In this conformation the xylo-configuration betwen C-2 and C-4 is extended by *gauche* orientations of 5-OH and 6-OH, stabilized

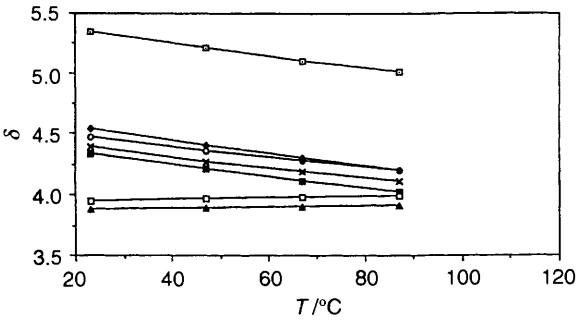

Fig. 6 Diagram of temperature coefficients $d\delta/dT$ of hydroxy protons as well as of the methine hydrogens 2-H and 3-H of gluconamide **3**: ⊡, 2-OH; ×, 3-OH; ○, 4-OH; ◆, 5-OH; ■, 6-OH; □, 2-H; ▲, 3-H

by *anti*-parallel orientations of 5-H and 4-OH as well as between one of the methylene hydrogens at C-6 and 5-OH (Fig. 4). The repulsive O-2//O-4 interaction is thus overcompensated by four attractive O/O *gauche* positions. This conclusion agrees with an estimate of interaction energies. Each *syn*-diaxial O//O interaction raises the conformational energy by about 8.0 kJ mol^{-1},[14] whereas the rearrangement from *anti* to *gauche* of vicinal oxygens results in an energy gain of −2.1 kJ mol^{-1}.[22,42] The alternative $_4G^-$ sickle, however, introduces another repulsive O//O interaction between O-3 and O-5 and costs an extra 8.0 kJ mol^{-1}. Besides the stabilizing *anti* relationship between 5-H and 4-OH is removed. Other possible sickle conformations destroy the xylo-conformation between C-2 and C-4 and the *anti* position between 4-OH and 5-OH is also preserved or a second bent within the head group is required.

The planar conformation of talonamide **4** contains the ribo-configuration with hydroxy groups 2-OH, 3-OH and 4-OH in unfavourable *anti*-position, which could not be stabilized by stereoelectronic interactions. Only within the terminal region of the head group *gauche* arrangements between 4-OH, 5-OH and 6-OH occur, stabilized by *anti*-parallel C-H bonds (Figs. 3 and 4). A sickle conformation is thus only favoured between C-2 and C-4. Here the removal of a *syn*-diaxial O//O interaction is accompanied by an additional *gauche* arrangement of oxygen atoms. Rotation around the C-1–C-2 axis is, however, highly hindered because of the partial π-character of the bonds neighbouring the amide group, resulting from the *gauche* orientation of 2-OH to the carbonyl group.[43] Clockwise rotation around the C-3–C-4 axis produces an O-3//O-5 arrangement, the alternative rotation a C-2//O-5 orientation. An analogous C-1//O-4 interaction occurs within the $_2G^-$ sickle conformation. There only remains the $_2G^+$ sickle conformation, which has been derived from the NMR results. It is free of both, O//O or C//O interactions and it contains an additional *gauche*-oriented pair of oxygens (O-2/O-3) with a stabilizing *anti*-parallel C-H bond (Figs. 3, 4). Furthermore, the oxygen atoms O-2 and O-6 are in the plane of the carbon atoms C-2 to C-6, thus occupying a sterically preferred arrangement.[44]

The solution conformation of gulonamide **5** corresponds to the xylo-configuration between C-3, C-4 and C-5, probably extended by a *gauche* position of 6-OH, as was evidenced by coupling constants of 4.6 or 5.7 Hz respectively (Table 2). An optimized conformation is obtained by rotation around the C-2–C-3 bond. This removes the *anti* position between 2-OH and 3-OH. Clockwise rotation, however, results in a C-1//O-4 interaction and counterclockwise rotation produces an O-2//O-4 repulsion. Both unfavourable interactions as well as the incomplete compensation of the O-3//O-5 repulsion by only three *gauche*-orientated oxygen pairs destabilizes all conformations in DMSO solution.

The conformations of hexonamides **3**–**5** thus can be traced back unequivocally to both repulsion between 1,3-*syn*-diaxial arrangement of carbon and oxygen atoms, as well as to attractive *gauche* interactions between oxygen atoms of neighbouring carbon atoms. The same assumption holds for galacton- and mannon-amides **1** and **2**. Within the planar conformations of both hexon head groups no O//O or C//O arrangement occurs. Such repulsive 1,3-arrangements would, however, result if further *gauche*-oriented pairs of oxygens should be created by rotations around any of the C–C bonds. Clockwise rotation around the C-2–C-3 axis of mannonamide **2**, for example, produces an O-2//O-4 interaction, whereas the counterclockwise movement gives a C-1//O-4 arrangement. Rotation around the C-4–C-5 bond gives the $_4G^-$ and $_4G^+$ sickles with 1,3-*syn* oxygen and carbon atoms, analogous to gluconamide **3**. Here only three pairs of *gauche* oxygens compensate for the repulsion. These sickle conformations of **2** are thus energetically unfavoured in polar solvents, but in apolar medium a sickle conformation may occur, because the stabilizing energy of *gauche*-positioned oxygens raises to −3.7 kJ mol^{-1}.[22] This consideration is supported by molecular dynamics simulations of mannitol, which favoured a planar conformation in water and any sickle conformation in apolar media.[45]

More subtle effects concern the relative mobilities of the molecular fragments. The central C-3–C-4 bond is practically blocked in all five cases. The 'inner' C-2–C-3 and the 'outer' C-4–C-5 bonds are more flexible, except for galactonamide **1**. The amide end with the long alkyl chain obviously does not slow down rotational movements. Finally it was found that both, gluconamide **3** and gulonamide **5**, are somewhat flexible at both ends of the head groups. Nevertheless, only gluconamide **3** aggregates to form highly curved micellar fibres in aqueous solution, whereas gulonamide **5** yields planar bilayers. It is thus not possible to determine molecular assemblies from conformations of dissolved monomers. The *gauche* effect, which is all-important in solution is obviously wiped out in large assemblies.

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