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The Structure of Glycosyl Amides: A Combined Study by NMR Spectroscopy, X-Ray Crystallography, and Computational Chemistry

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Abstract: The structure of *N*-formyl, *N*-acetyl-*N*-methyl, and *N*-acetyl glycosylamines has been studied by NMR spectroscopy in solution, single crystal X-ray diffractometry, and corroborated by PM3 semiempirical calculations. The results quite agree with an *anti* conformation around the glycosydic bond for these substances.

INTRODUCTION

While the role of glycoconjugates in a series of varied processes such as molecular recognition, cell adhesion, or enzyme inhibition among others has been widely recognized,[2] the accurate determination of these structures which will be ultimately responsible for their function and properties, is far from being fully understood. Thus, the amide function is present not only in numerous glycopeptides[2] and glycolipids[3] but also in naturally-occurring carbohydrate antibiotics such as istamycins[4] and calicheamicins.[5] NMR spectra of these substances usually exhibit two signal sets, which at first glance may be attributed to the existence of *Z* and *E* isomers as a consequence of the restricted rotation around the CO–N bond. A few years ago we proposed a set of NMR rules that have allowed us to assign the preferred geometry of a wide range of amido- and thioamidosugars classed together in series I-III (Table 1).[6] For compounds of series III (Sugar-NH-CRX), only one signal set is observed and attributable to *Z* isomers. It has been quite gratifying to see how these empirical rules have been successfully used by other colleagues and ourselves to effect the configurational assignment of numerous *N*-acylaminosugars.[7]

The spectroscopic behavior of amidosugars emerges from the magnetic anisotropy originated by the amide function. In the classical model proposed by Paulsen and Todt,[8] it is possible to visualize the substituents around the planar amide bond as two conical regions that tilt up and down (Figure 1). NMR resonances show

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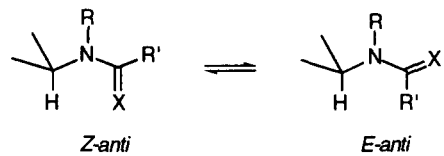
that a substituent located at the **a** position is more shielded than **a'**. In the case of amides of series I and II which exist in solution in *Z-anti* and *E-anti* configurations, and for those of series III in *Z-anti*, the sugar proton geminal to the amide group is found in the relative dispositions **a'** (*Z-anti*) and **a** (*E-anti*), thereby accounting for the different chemical shifts observed.[6]

Table 1. Rules for configurational assignment of amides and thioamides (X = O, S) of series I and II.[6]

serie I, Sugar-NH-CHX	*serie II, Sugar-NR-CRX*
$\delta_{H(sugar)}$ (*Z*) > $\delta_{H(sugar)}$ (*E*) $\delta_{C(sugar)}$ (*Z*) < $\delta_{C(sugar)}$ (*E*) δ_{CX} (*Z*) < δ_{CX} (*E*) δ_{CHX} (*Z*) > δ_{CHX} (*E*) $J_{NH,CHO}$ ~0 (*Z*); $J_{NH,CHO}$ = 9.2-11.3 (*E*) $J_{NH,CHS}$ =5.0-6.1 (*Z*); $J_{NH,CHS}$ = 9.5-14.1 (*E*)	$\delta_{H(sugar)}$ (*Z*) > $\delta_{H(sugar)}$ (*E*) $\delta_{C(sugar)}$ (*Z*) < $\delta_{C(sugar)}$ (*E*) δ_{CX} (*Z*) > δ_{CX} (*E*) When R = sat. alkyl group: δ_{CXCH_3} (*Z*) < δ_{CXCH_3} (*E*) When R = benzyl group: δ_{CXCH_3} (*Z*) > δ_{CXCH_3} (*E*)



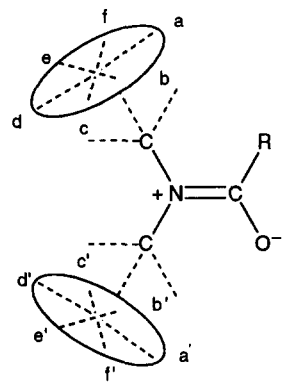


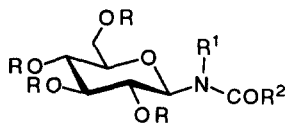
Figure 1. Magnetic anisotropy of amides after Paulsen and Todt.[8]

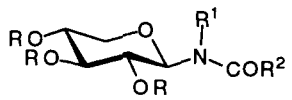
It is assumed that the conformation around the glycosidic bond plays an important role in the biological properties of carbohydrate derivatives. Thus, the stable conformations found in *C*-glycosides have been frequently attributed to steric effects.[9] *N*-nucleosides adopt at the anomeric position intermediate dispositions between the extreme *syn* and *anti* conformations.[10] The conformation of aglycones in *O*-glycosides can be associated with the existence of anomeric[11,12] and *exo*-anomeric effects.[13] However, these conformations are far from a coplanar disposition between the glycosidic proton and the amide group. Moreover, in the light of NMR experiments,[6] conformations other than *anti* cannot be excluded. It is therefore necessary to conduct a further study, especially by unequivocal solid state X-ray analysis and corroborated by theoretical estimations of the energetic barriers, in order to confirm the empirical correlations established by NMR spectroscopy. In this

context, we were encouraged by previous results on glycoamidines, for which semiempirical calculations support the conformational assignments obtained by ^{1}H- and ^{13}C-NMR.[14] In the case of glycosyl amides, the optimization of geometries and heats of formation has also been estimated using the MNDO-PM3 method.[15,16]

RESULTS AND DISCUSSION

Syntheses. For this study we have prepared the glycosyl amides **1-10** bearing simple substituents (H or Me) in order to facilitate the further computation of such structures. Unprotected derivatives (*e.g.* **2**, **5**, **6**, **9**, and **10**) have also been included for comparative purposes, because these substances had not been previously examined.[6]

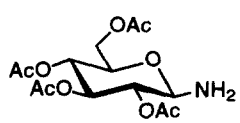




1 R = Ac, R^1 = R^2 = H
2 R = R^1 = R^2 = H
3 R = Ac, R^1 = R^2 = Me
5 R = H, R^1 = R^2 = Me
7 R = Ac, R^1 = H, R^2 = Me
9 R = R^1 = H, R^2 = Me

4 R = Ac, R^1 = R^2 = Me
6 R = H, R^1 = R^2 = Me
8 R = Ac, R^1 = H, R^2 = Me
10 R = R^1 = H, R^2 = Me

Compound **1** was synthesized by reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (**11**)[17] with acetic formic anhydride.[18] Glycosyl amides **3** and **4** were prepared by acetylation of *N*-methyl-β-D-glucopyranosylamine (**12**) or -xylopyranosylamine (**13**), respectively. Likewise, **12** and **13** were prepared by reaction of the corresponding aldoses with a 33% ethanolic solution of methylamine, an advantageous protocol over the previous syntheses described by Masciorini and coworkers.[19] Finally, the glycosyl amides **7** and **8** were prepared according to the method by Isbell and Frush.[20] Deprotection of hydroxyl groups was conducted by following the literature protocols yielding **2**[21], **5**[19], **6**[19], **9**[20], **10**[20], although with some modifications to favor the crystallization of these substances (see experimental).



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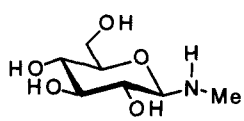

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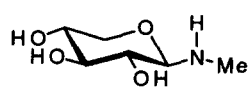

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NMR Spectroscopy. Table 2 shows the most important proton and carbon resonances of compounds **1-10**. As expected, either *O*-protected or unprotected glycosyl amides follow the general behavior observed previously for similar amidosugars.[6] Compounds **1-6** showed two signal sets although chemical shifts were largely dependent on the solvent (Table 2).

Table 2. Selected NMR data for compounds **1-10**

Compound	Solvent	δ H-1	δ C-1	δ NCO	δ NC*H*O	δ NCX*C*H$_3$	$J_{NH,H-1}$	$J_{NH,CHO}$	δ NC*H*$_3$	δ NC*H*$_3$
1*Z*	$CDCl_3$	5.33t	76.5	161.2	8.26s		9.3	~0		
1*E*	$CDCl_3$	4.73t	81.9	163.6	8.22d		10.5	10.5		
2*Z*	DMSO-d_6	4.76t	77.8	161.5	8.07s		9.0	~0		
2*E*	DMSO-d_6	4.35t	83.6	165.2	8.07d		9.5	10.2		
2*Z*	DMSO-d_6+D_2O	4.80d			8.11s					
2*E*	DMSO-d_6+D_2O	4.44d			8.11s					
2*Z*	C_5D_5N	4.58t	79.2	162.4	7.45-7.40m		8.8	~0		
2*E*	C_5D_5N	3.83t	84.7	165.8	7.45-7.40m		9.6	9.6		
2*Z*	C_5D_5N+D_2O	4.84d			7.77s					
2*E*	C_5D_5N+D_2O	4.21d			7.76s					
3*Z*	$CDCl_3$	5.87d	79.58						2.93	29.87
3*E*	$CDCl_3$	5.01d	85.40						2.85	27.14
4*Z*	$CDCl_3$	5.78d	80.24						2.91	29.83
4*E*	$CDCl_3$	5.05-4.92m	86.03						2.85	27.05
5*Z*	D_2O	5.39d	82.44	177.05		22.34			2.92	30.63
5*E*	D_2O	4.90d	87.38	176.09		21.56			2.78	27.76
6*Z*	DMSO-d_6+D_2O	5.16d							2.79	
6*E*	DMSO-d_6+D_2O	4.60d							2.66	
6*Z*	DMSO-d_6		82.45	171.37		22.55				29.64
6*E*	DMSO-d_6		87.75	170.84		21.80				26.46
7*Z*	$CDCl_3$	5.29t	78.04			23.26	9.3			
8*Z*	$CDCl_3$	5.20t	78.54			23.12	9.3			
9*Z*	DMSO-d_6	4.69t	79.46	169.76		22.90	9.1			
9*Z*	D_2O	4.91t	80.41	176.68		23.37				
10*Z*	DMSO-d_6	4.60t	80.51	170.15		23.05	9.0			
10*Z*	DMSO-d_6+D_2O	4.57d	81.09	173.38		23.57				
10*Z*	C_5D_5N	5.62t	81.95	170.82		23.33	9.0			

The resonances of H-1 and C-1 can be easily identified and have diagnostic value for the assignment of both isomers, which show large variations in the chemical shifts (Δδ). For unprotected amides **2**, **5**, and **6** the N-CO group was more deshielded for *E* than for *Z* isomers. This is also true for *O*-protected glycosylamides, although the assignment was often complicated by the presence of ester groups. Likewise, the methyl group of the NCXMe moiety resonated further downfield for *Z* than for *E* isomers. In the case of compound **2**, the N-CHO protons showed the same or similar shifts for both isomers and consequently the assignment of this signal can sometimes be difficult. Coupling constants also provided a valuable information for the assignment of *Z*/*E* configurations. $J_{NH,CHO}$ exhibited larger values for *E* (~9.5-10.5 Hz) than for *Z* isomers (~0 Hz). However, the values of $J_{NH,H-1}$ were not able to discriminate between *syn*- and *anti*-periplanar conformations.[6]

Derivatization procedures such as methylation, acetylation, or trimethylsilylation constitute current strategies that facilitate the structural characterization of polysaccharides.[22] We have therefore considered the spectroscopic behavior of *N*-methyl amidosugars. Although a general tendency could not be found,[6] for

compounds **3-6** the N-Me group (both the proton and carbon resonances) was more deshielded for *Z* than for *E* isomers. The *N*-monosubstituted amides **7-10** showed only one signal set, even at low temperatures, as evidenced by the analysis of **10** in C_5D_5N at 240 K. In agreement with *O*-acyl derivatives,[6] the chemical shift of H-1 for compound **9** (4.69 ppm, DMSO-d_6) was similar to that of this proton in the *Z* isomer of **2** (4.76 ppm, DMSO-d_6).

Table 3 also displays the relative populations of *Z* and *E* isomers. In the case of the *N*-formyl derivative **2** the *Z* isomer was prevalent, while for unprotected *N*-methyl amidosugars **5** and **6** the major isomers had *E* configurations in the range of solvents studied. Thus, spectroscopic data of compounds **1-10** are consistent with *Z-anti* or *E-anti* configurations in accordance with other amidosugars.[6]

Table 3. Populations of *Z/E* isomers for compounds **1-10**

Compound	Solvent	*Z/E* ratio
1	$CDCl_3$	100/50
2	DMSO-d_6	100/71
2	DMSO-d_6+D_2O	100/60
2	C_5D_5N	100/70
2	C_5D_5N+D_2O	100/42
3	$CDCl_3$	100/41
4	$CDCl_3$	100/50
5	D_2O	81/100
6	DMSO-d_6	48/100
6	DMSO-d_6+D_2O	62/100
7	$CDCl_3$	100/0
8	$CDCl_3$	100/0
9	DMSO-d_6 or D_2O	100/0
10	DMSO-d_6 or C_5D_5N	100/0

X-Ray Crystallography. Structural analyses by this technique reveal the stable conformers in the solid state, so that for comparative purposes with equilibria in solution, crystallographic diagrams are extremely useful. Glycosyl amides with different substitution patterns have been subjected to X-ray diffractometry.[23]

No satisfactory crystals could be obtained for the unprotected derivative **2**. However, the crystal structure of **1** with atom numbering is presented in Figure 2. Some hydrogen atoms have been omitted for the sake of clarity. X-Ray crystallographic data show an *anti*-periplanar conformation of the *Z* configuration, which is in accordance with the structure of the major isomer in $CDCl_3$ solution (Table 3). In contrast, *N*-methyl xylopyranosylamine **6** adopts the *E* configuration in the solid state (Figure 3), which agrees with the preferred structure in solution. In the case of *N*-monosubstituted glycosyl amides, suitable crystals could be obtained for *O*-protected (**8**) and unprotected (**9**) derivatives (Figures 4 and 5, respectively). Again, the crystalline structure reveals the greater stability of *Z* isomers, which corresponds with the situation found in solution.

Table 4 also shows the most representative dihedral angles for a common structural arrangement for compounds **1**, **6**, **8** and **9**. In all the cases mentioned the solid state structure shows a conformation around the glycosidic position close to an *anti*-periplanar disposition. Heavy atoms are in a nearly coplanar arrangement according to the values of dihedral angles such as C_1-N-C_2-O_2 and C_1-N-C_2-B, whereas major deviations (up to 30°) were found for dihedral angles involving hydrogen positions.

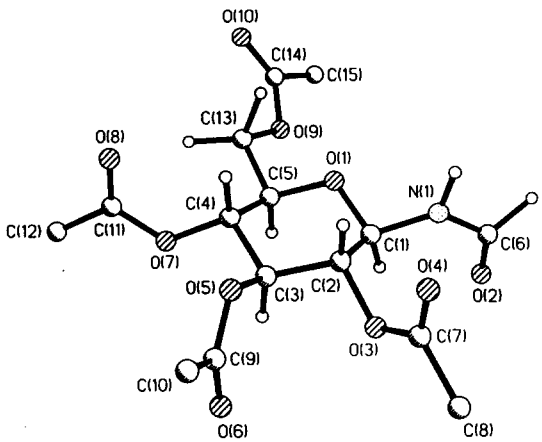


Figure 2. Molecular structure of compound **1**

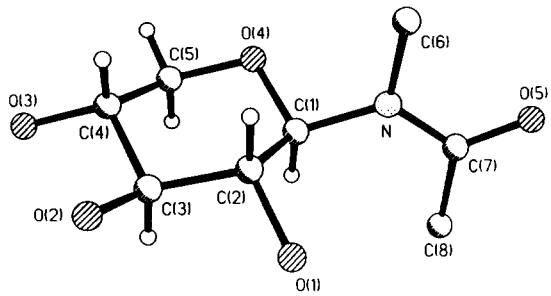


Figure 3. Molecular structure of compound **6**

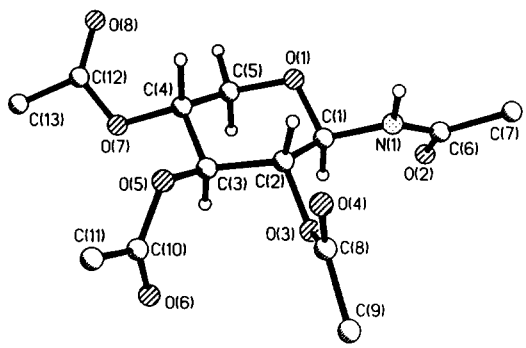


Figure 4. Molecular structure of compound **8**

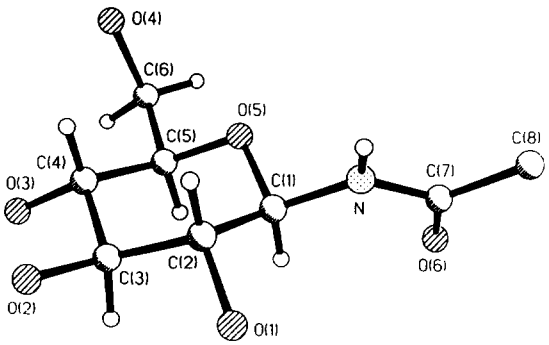
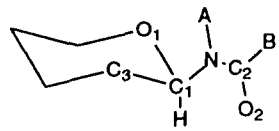


Figure 5. Molecular structure of compound **9**

Table 4. Selected dihedral angles from X-ray diffraction analyses



1, A = B = hydrogen
6, A = B = carbon
8 and **9**, A = hydrogen, B = carbon

Angle/Compound	1	6	8	9
H-C_1-N-A	159.4	165.3	-154.7	-170.2
H-C_1-N-C_2	-1.2	-16.5	23.2	29.7
C_1-N-C_2-B	164.6	-0.9	-178.7	177.4
C_1-N-C_2-O_2	-3.1	-179.6	1.5	-4.1
A-N-C_2-O_2	-167.0	-1.4	179.4	-162.0
A-N-C_2-B	0.7	177.2	-0.8	19.5

Semiempirical Calculations. The semiempirical MNDO-PM3 method[15,16] has been utilized for the optimization of geometries and the calculations of heats of formation as a function of the dihedral angle Φ, in the cases of compounds **2**, **5**, **9** and for models **14-16** (Figures 6-8). The starting value of Φ = 0° refers to a conformation for which the bonds C_1-H_1 and C=O are eclipsed. Calculations were performed assuming rotations with 30° increments around the glycosidic bond with full optimization for the rest of parameters of the amide group. The sugar moiety was fixed in a conformation whose energy was minimized previously. In the above-mentioned structures, two conformational minima are located close to 0° and 180° and energy maxima around 120° and 270°.

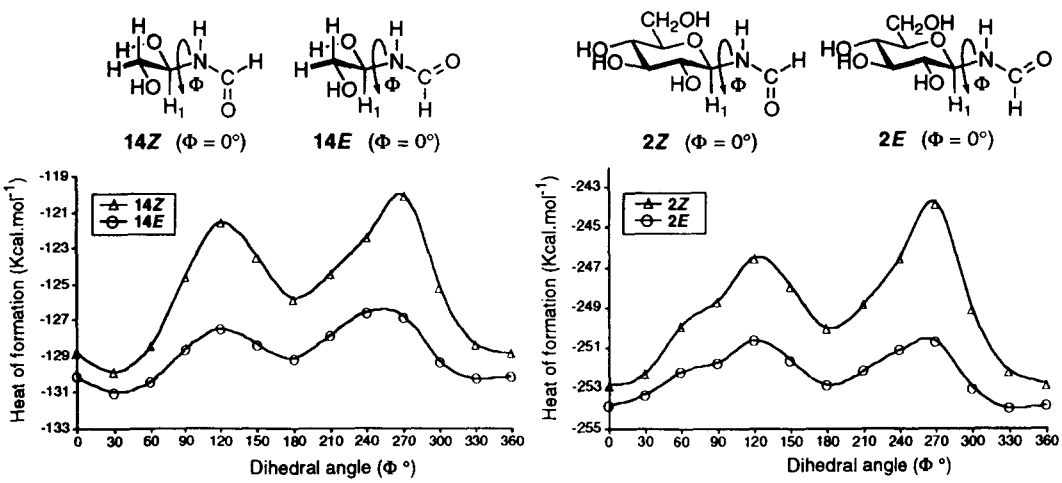


Figure 6. Heats of formation *versus* the dihedral angle Φ for the conformational equilibrium of compound **2** and model **14**

The calculations do not predict significant differences between *Z* and *E* isomers, not even in the case of formamides, because the energy differences are close to the experimental error. This observation agrees with the situation found in solution and thus, NMR spectra of formamides **1** and **2**, or *N*-disubstituted amidosugars **3-6**

exhibit two signal sets. However, the theoretical results for compound **9**, or the model **16**, are surprising since *N*-monosubstituted amidosugars exist as single isomers as evidenced by NMR analyses. It is also worthwhile to note that in all the cases the minima correspond with an *anti*-periplanar conformation ($\Phi = 0°$), though in the particular case of the *E*-isomer of **2** the difference with a synperiplanar conformation ($\Phi = 180°$) is very small (Figure 6).

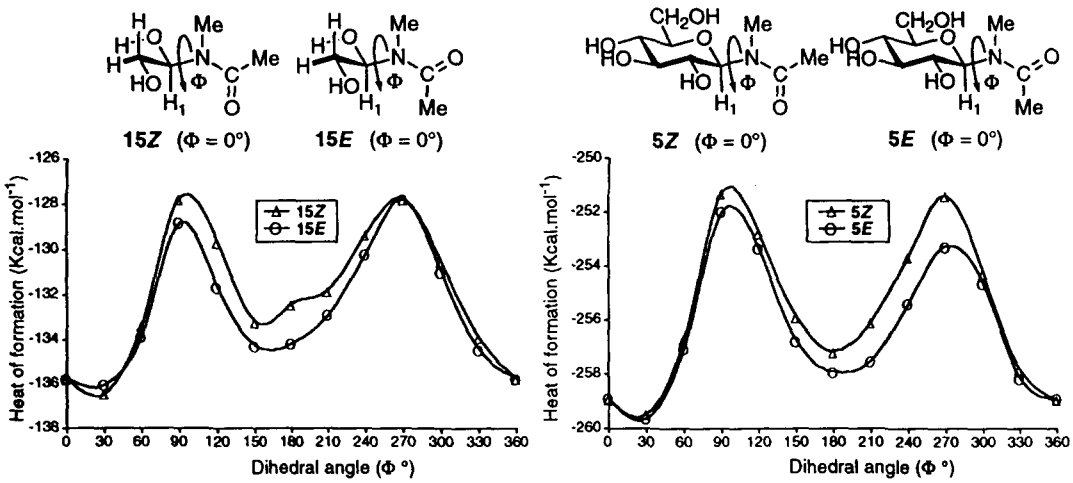


Figure 7. Heats of formation *versus* the dihedral angle Φ for the conformational equilibrium of compound **5** and model **15**

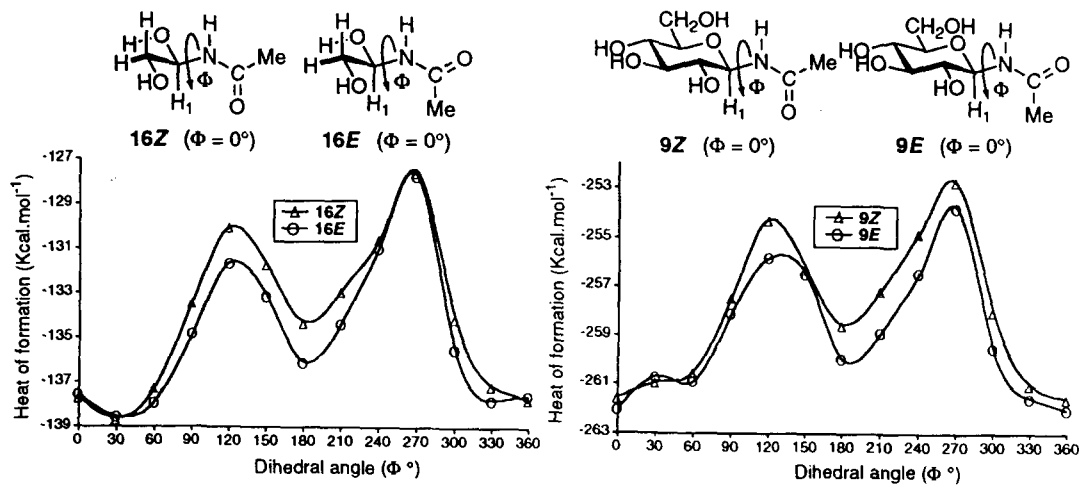


Figure 8. Heats of formation *versus* the dihedral angle Φ for the conformational equilibrium of compound **9** and model **16**.

In conclusion the present study demonstrates for the first time, in an unequivocal fashion, that glycosyl amides exist preferentially as *anti* isomers around the glycosidic bond, both in solution and in the solid state. Furthermore, these data have been supported by semiempirical calculations.

EXPERIMENTAL

General Methods. All solvents were purchased from commercial sources and used as received unless otherwise stated. The reactions and the purities of compounds were monitored by TLC performed on precoated silica gel plates with a fluorescent indicator (Merck 60 GF_{254}). Melting points were determined on an Electrothermal apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C on a Perkin-Elmer 241 polarimeter at 589 (D-line), 578, 546, 436, and 365 nm. IR spectra were recorded on Perkin-Elmer 399 and FT-IR MIDAC spectrophotometers. Solid samples were recorded on KBr (Merck) pellets. ^{1}H- (400 and 200 MHz) and ^{13}C-NMR (100 and 50.3 MHz) spectra were recorded on Bruker AC 200-E and Bruker 400 AC/PC spectrometers in different solvent systems. Assignments were confirmed by homo- and hetero-nuclear double-resonance, DEPT (distortionless enhancement by polarization transfer), and variable temperature experiments. Some coupling constants could be measured after D_2O exchange. TMS was used as the internal standard (δ = 0.00 ppm) and all J values are given in Hz. X-Ray data were collected on a Siemens P4 automatic diffractometer at 298 K, using Mo-Kα radiation (λ = 0.71073 Å) monochromatized by a highly oriented graphite crystal. The crystal stability was monitored using three standard reflections every 97 reflections and the data were scaled accordingly. Data were collected employing the 2θ-θ scan technique in the range $2.0° < 2\theta < 60.0°$ for compounds **1** and **8**, $2.0° < 2\theta < 55.0°$ for compound **6**, and $1.0° < 2\theta < 60.0°$ for compound **9**. The structures were solved by direct methods (SHELXTL.IRIS) and refined by full-matrix least squares. Geometry optimizations and heats of formation were estimated using the semiempirical method[15,16] MNDO-PM3 (Modified Neglected of Diatomic Overlap-Parametric Method 3),[16] based on the NDDO approach (Neglect of Diatomic Differential Overlap) from MOPAC programs[24] and implemented in the Convex 210 computer of the University of Extremadura. The methodology for determining the heats of formation as function of dihedral angles has been described above.

2,3,4,6-Tetra-*O*-acetyl-*N*-formyl-β-D-glucopyranosylamine (1).[25] To a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine[17] **11** (1.0 g, 2.9 mmol) in ethyl acetate (8 mL) was added acetic formic anhydride (2.4 mL), and the reaction mixture was kept at room temperature for 6 h. The solvent was evaporated to dryness and the residue was crystallized from ethanol (0.7 g, 62%). M.p. 145-147 °C; $[\alpha]_{578}$ +20° (*c* 0.5, $CHCl_3$), [literature:[25] m.p. 147-148 °C; $[\alpha]_{578}$ +21° (*c* 0.5, $CHCl_3$). NMR spectra have also been previously described.[6,25]

***N*-Formyl-β-D-glucopyranosylamine (2).**[21] To a solution of **1** (0.5 g, 1.3 mmol) in methanol (2.5 mL) was added 1M sodium methoxide (0.15 mL) and, after 24 h at 4 °C the reaction mixture was neutralized with Dowex 50W (H^+). The mixture was filtered and the resulting solution was evaporated to give a white solid (0.2 g, 64%), m.p. 182-183 °C (dec.); $[\alpha]_D$ -2°, $[\alpha]_{578}$ -3°, $[\alpha]_{546}$ -3°, $[\alpha]_{436}$ -5°, $[\alpha]_{365}$ -6° (*c* 0.5, H_2O); δ_H (DMSO-d_6, *Z* isomer) 8.57 (d, 1H, NH), 8.07 (s, 1H, CHO), 5.13-4.94 (m, 3OH), 4.76 (t, 1H, $J_{1,2}$ 9.0, $J_{1,NH}$ 9.0, H-1), 4.60-4.53 (m, OH), 3.64 (m, 1H, H-6), 3.41 (m , 1H, H-6') and 3.18-3.03 (m, 4H, H-2, H-3, H-4, H-5); (DMSO-d_6, *E* isomer) 8.37 (t , 1H, $J_{1,NH}$ =$J_{NH,CHO}$ 10.2, NH), 8.07 (d, 1H, CHO), 4.35 (t, 1H, $J_{1,2}$ 8.9, H-1) and 3.18-3.03 (m, 4H, H-2, H-3, H-4, H-5); (DMSO-d_6 + D_2O, *Z* isomer) 8.11 (s, 1H, CHO), 4.80 (d, 1H, $J_{1,2}$ 9.0, H-1), 3.69 (m, 1H, H-6), 3.48 (m, 1H, H-6'), 3.31-3.23 (m, 1H, H-5), 3.31-3.10 (m, 2H, H-3, H-4), 3.18-3.10 (m, 1H, H-2); (DMSO-d_6 + D_2O, *E* isomer) 8.11 (s, 1H, CHO), 4.44 (d, 1H, $J_{1,2}$ 8.8, H-1), 3.69 (m, 1H, H-6), 3.48 (m, 1H, H-6'), 3.31-3.23 (m, 1H, H-5), 3.31-3.10 (m, 2H, H-3 and H-4), 3.18-3.10 (m, 1H, H-2); (C_5D_5N, *Z* isomer) 8.70 (d, 1H, $J_{1,NH}$ 8.8, $J_{NH,CHO}$ ~0, NH), 7.45-7.40 (m, 1H, CHO), 4.58 (t, 1H, $J_{1,2}$ 9.0, H-1); (C_5D_5N, *E* isomer) 8.66 (t , 1H, $J_{1,NH}$ =$J_{NH,CHO}$ 9.6, NH), 7.45-

7.40 (m, 1H, CHO), 4.83 (t, 1H, $J_{1,2}$ 9.1, H-1); (C_5D_5N+ D_2O, Z isomer) 7.77 (s, 1H, CHO), 4.84 (d, 1H, $J_{1,2}$ 9.0, H-1); (C_5D_5N+ D_2O, *E* isomer) 7.76 (s , 1H, CHO), 4.21 (d, 1H, $J_{1,2}$ 9.1, H-1); δ_C (DMSO-d_6, *Z* isomer) 161.5 (CHO), 77.8 (C-1), 78.5, 77.3, 72.4, 69.8 (C-3, C-5, C-2, C-4), 60.8 (C-6); δ_C (DMSO-d_6, *E* isomer) 165.2 (CHO), 83.6 (C-1), 78.4, 77.2, 72.1, 69.8 (C-3, C-5, C-2, C-4), 60.9 (C-6); δ_C (C_5D_5N, *Z* isomer) 162.4 (CHO), 79.2 (C-1), 78.9, 78.4, 73.4, 70.6 (C-3, C-5, C-2, C-4), 61.7 (C-6); δ_C (C_5D_5N, *E* isomer) 165.8 (CHO), 84.7 (C-1), 78.9, 78.1, 73.3, 70.5 (C-3, C-5, C-2, C-4), 61.6 (C-6).

***N*-Acetyl-2,3,4,6-tetra-*O*-acetyl-*N*-methyl-β-D-glucopyranosylamine (3).**[19] A suspension of *N*-methyl-β-D-glucopyranosylamine (**12**, 2.0 g, 10.4 mmol) in pyridine (14 mL) and acetic anhydride (14 mL), was stirred at 0 °C for 4 h and then kept at room temperature for 48 h. The reaction mixture was poured into ice-water (200 mL) and extracted with chloroform (3 x 100 mL). The organic layer was washed successively with 3M hydrochloric acid (3 x 100 mL), sodium hydrogencarbonate saturated solution (3 x 100 mL) and water (3 x 100 mL), dried over anhydrous magnesium sulfate and evaporated to afford a white solid that was crystallized from ethanol (2.8 g, 66%); m.p. 111-113 °C, $[\alpha]_D$ +45°, $[\alpha]_{578}$ +46°, $[\alpha]_{546}$ +53°, $[\alpha]_{436}$ +91°, $[\alpha]_{365}$ +144° (*c* 0.5, $CHCl_3$), [literature:[19] m.p. 107-109 °C, $[\alpha]_D$ +44° (*c* 1, $CHCl_3$)]; ν_{max} 1740 (CO, ester) and 1665 cm^{-1} (C=O, amide); δ_H ($CDCl_3$, *Z* isomer) 5.87 (d, 1H, $J_{1,2}$ 9.5, H-1), 5.33 (t, 1H, $J_{2,3}$=$J_{3,4}$ 9.5, H-3), 5.08 (t, 1H, H-2), 5.05 (t, 1H, $J_{4,5}$ 9.7, H-4), 4.22 (dd, 1H, $J_{5,6}$ 4.8, H-6), 4.12 (dd, 1H, $J_{5,6'}$ 2.0, $J_{6,6'}$ 12.4, H-6'), 3.83 (m, 1H, H-5), 2.93 (s, 3H, NMe), 2.08, 2.04, 2.01, 2.00 (4s, 15H, 5OAc); δ_H ($CDCl_3$, *E* isomer) 5.30 (t, 1H, $J_{3,4}$ 9.4, H-3), 5.01 (d, 1H, $J_{1,2}$ 9.2, H-1), 5.22 (t, 1H, $J_{2,3}$ 9.4, H-2), 5.10 (t, 1H, $J_{4,5}$ 9.9, H-4), 4.24 (dd, 1H, $J_{5,6}$ 5.0, H-6), 4.15 (dd, 1H, $J_{5,6'}$ 2.1, $J_{6,6'}$ 13.0, H-6'), 3.80 (m, 1H, H-5), 2.85 (s, 3H, NMe), 2.18, 2.11, 2.05, 2.02 (4s, 15H, 5OAc); δ_C ($CDCl_3$, *Z* isomer) 171.9, 170.6, 169.8, 169.6 (NCO and OCO), 79.6 (C-1), 74.0 (C-5), 73.2 (C-3), 68.4 (C-2), 68.3 (C-4), 62.0 (C-6), 29.9 (NMe), 22.2, 20.7, 20.6 (NCOMe and OCOMe); δ_C ($CDCl_3$, *E* isomer) 170.1, 169.9, 169.3, 168.9 (NCO and OCO), 85.4 (C-1), 74.2 (C-5), 73.3 (C-3), 68.5 (C-2), 68.0 (C-4), 62.0 (C-6), 27.1 (NMe), 21.7 (NCOMe or OCOMe).

***N*-Acetyl-2,3,4-tri-*O*-acetyl-*N*-methyl-β-D-xylopyranosylamine (4).**[19] Starting from *N*-methyl-β-D-xylopyranosylamine (**13**, 3.0 g, 18.4 mmol) and following the same protocol described for **12**, the title compound was obtained (3,7 g, 61%); m.p. 121-123 °C; $[\alpha]_D$ +36°, $[\alpha]_{578}$ +37°, $[\alpha]_{546}$ +43°, $[\alpha]_{436}$ +79°, $[\alpha]_{365}$ +137° (c 0.5, $CHCl_3$), [literature:[19] 124-126 °C, $[\alpha]_D$ +38°, (*c* 2.5, $CHCl_3$)]; ν_{max} 1730 (C=O, ester) and 1650 cm^{-1} (C=O, amide); δ_H ($CDCl_3$, *Z* isomer) 5.78 (d, 1H, $J_{1,2}$ 9.4, H-1), 5.34 (t, 1H, $J_{2,3}$=$J_{3,4}$ 9.6, H-3), 5.05-4.92 (m, 1H, H-4), 5.04 (t, 1H, H-2), 4.09 (dd, 1H, $J_{4,5}$ 5.7, H-5), 3.45 (t, 1H, $J_{4,5'}$ 11.6, $J_{5,5'}$ 11.6, H-5'), 2.91 (s, 3H, NMe), 2.08, 2.05, 2.03, 2.01 (4s, 12H, 4OAc); δ_H ($CDCl_3$, *E* isomer) 5.31 (t, 1H, $J_{3,4}$ 9.2, H-3), 5.16 (t, 1H, $J_{1,2}$ =$J_{2,3}$ = 9.2, H-2), 5.05-4.92 (m, 2H, H-1, H-4), 4.18 (dd, 1H, $J_{4,5}$ 5.6, $J_{5,5'}$ 11.4, H-5), 3.42 (t, 1H, $J_{4,5'}$ 11.0, H-5'), 2.85 (s, 3H, NMe), 2.17, 2.06, 2.05, 2.00 (4s, 12H, 4OAc); δ_C ($CDCl_3$, *Z* isomer) 171.9, 169.9, 169.7 (NCO and OCO), 80.2 (C-1), 72.8 (C-3), 69.0 (C-4), 68.5 (C-2), 64.8 (C-5), 29.8 (NMe), 22.2, 20.6, 20.5, 20.4 (NCOMe and OCOMe); δ_C ($CDCl_3$, *E* isomer) 170.6, 170.1, 168.1 (NCO and OCO), 86.0 (C-1), 72.9 (C-3), 69.0 (C-4), 68.6 (C-2), 65.0 (C-5), 27.1 (NMe), 21.6, 20.6, 20.5, 20.4 (NCOMe and OCOMe)

***N*-Acetyl-*N*-methyl-β-D-glucopyranosylamine (5).**[19] To a solution of *N*-acetyl-2,3,4,6-tetra-*O*-acetyl-*N*-methyl-β-D-glucopyranosylamine (**7** , 0.5 g, 1.2 mmol) in methanol (3 mL) was added 0.1M sodium methoxide (0.3 mL), and the reaction mixture was stirred at room temperature for 2 h. Then it was neutralized with Dowex 50W (H^+), filtered and evaporated to dryness to give a white solid (0.2 g, 67%), m.p. 100-102 °C; $[\alpha]_D$ +5°, $[\alpha]_{578}$ +6°, $[\alpha]_{546}$ +6°, $[\alpha]_{436}$ +8° (*c* 0.5, H_2O), [literature:[19] $[\alpha]_D$ -4° (*c* 0.4, H_2O)]; ν_{max} 3300-3400 (OH) and 1610 cm^{-1} (C=O, amide); δ_H (D_2O, *Z* isomer) 5.39 (d, 1H, $J_{1,2}$ 8.8, H-1), 3.79 (dd, 1H, H-6),

3,66 (dd, 1-H, H-6'), 3.59-3.44 (m, 2H, H-2, H-3), 3.43 (m, 1H, H-5), 3.34 (t, 1H, H-4), 2.92 (s, 3H, NMe), 2.09 (s, 3H, NCOMe); δ_H (D_2O, *E* isomer) 4.90 (d, 1H, $J_{1,2}$ 8.7, H-1), 3.76 (dd, 1H, H-6), 3.65 (dd, 1-H, H-6'), 3.60 (t, 1H, H-4), 3.59-3.44 (m, 3H, H-2, H-3, H-5), 2.78 (s, 3H, NMe), 2.12 (s, 3H, NCOMe); δ_C (D_2O, *Z* isomer) 177.1 (NCO), 82.4 (C-1), 78.7 (C-5), 77.3, 70.5, 70.0 (C-2, C-3, C-4), 58.2 (C-6), 30.6 (NMe), 22.3 (NCOMe); δ_C (D_2O, *E* isomer) 176.1 (NCO), 87.4 (C-1), 78.6 (C-5), 77.0, 69.9, 69.8 (C-2, C-3, C-4), 61.2 (C-6), 27.8 (NMe), 21.6 (NCOMe).

***N*-Acetyl-*N*-methyl-β-D-xylopyranosylamine (6).**[19] This compound was obtained according to Masciorini *et al.*,[19] ν_{max} 3300-3400 (OH) and 1610 cm^{-1} (C=O, amide); δ_H (DMSO-d_6 + D_2O, *Z* isomer) 5.16 (d, 1H, $J_{1,2}$ 8.7, H-1), 3.70 (m, 1H, H-4), 3.31-3.16 (m, 4H, H-2, H-3, H-5, H-5'), 2.79 (s, 3H, NMe), 1.98 (s, 3H, NCOMe); δ_H (DMSO-d_6 + D_2O, *E* isomer) 4.60 (d, 1H, $J_{1,2}$ 8.3, H-1), 3.70 (m, 1H, H-4), 3.31-3.16 (m, 3H, $J_{4,5}$ 8.3, $J_{4,5'}$ 2.4, H-2, H-5, H-5'), 3.06 (t, $J_{2,3} = J_{3,4}$ = 10.8, H-3), 2.66 (s, 3H, NMe), 2.02 (s, 3H, NCOMe); δ_C (DMSO-d_6, *Z* isomer) 171.4 (NCO), 82.5 (C-1), 77.7, 69.8, 69.7 (C-2, C-3, C-4), 68.1 (C-5), 29.6 (NMe), 22.6 (NCOMe); δ_C (DMSO-d_6, *E* isomer) 170.1 (NCO), 87.8 (C-1), 77.5 , 70.2, 69.6 (C-2, C-3, C-4), 68.0 (C-5), 26.5 (N-Me), 21.8 (NCOMe).

***N*-Acetyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine (7).**[20] This compound was prepared in 86% yield according to the protocol described in the literature.[20] Its NMR spectra have also been previously reported.[6]

***N*-Acetyl-2,3,4-tri-*O*-acetyl-β-D-xylopyranosylamine (8).**[20] The conventional acetylation of xylopyranosylamine with acetic anhydride and pyridine gave **8** (88%); m.p. 174-176 °C (ethanol); $[\alpha]_D$ +28°, $[\alpha]_{578}$ +29°, $[\alpha]_{546}$ +33°, $[\alpha]_{436}$ +62°, $[\alpha]_{365}$ +112° (*c* 0.5, $CHCl_3$), [literature:[20] m.p. 172-173 °C; $[\alpha]_D$ +28.5° (*c* 2, $CHCl_3$)]; ν_{max} 3300 (NH), 1740 (C=O, ester) and 1670 cm^{-1} (C=O, amide); δ_H ($CDCl_3$) 6.77 (d, 1H, $J_{1,NH}$ = 9.3, NH), 5.30 (t, 1H, $J_{3,4}$ = 9.6, H-3), 5.20 (t, 1H, $J_{1,2}$ = 9.4, H-1), 5.00 (m, 1H, H-4), 4.92 (t, 1H, $J_{2,3}$ = 9.4, H-2), 4.08 (dd, 1H, $J_{4,5}$ = 5.7, H-5), 3.46 (t, 1H, $J_{4,5'}$ =11.3, $J_{5,5'}$ = 11.3, H-5'), 2.08, 2.05, 2.04, 2.01, 1.98 (5s, 15H, 5OAc); δ_C ($CDCl_3$) 170.9, 170.7, 169.8, 169.7 (NCO and OCO), 78.5 (C-1), 72.4 (C-3), 70.7 (C-2), 68.9 (C-4), 64.4 (C-5), 23.1 (NCOMe), 20.5, 20.4 (OCOMe).

***N*-Acetyl-β-D-glucopyranosylamine (9).**[20] To a solution of **7** (3.0 g, 7.7 mmol) in methanol (15 mL) was added 1M sodium methoxide (0.9 mL), and the reaction mixture was kept at 0 °C for 6 h. The resulting white solid was filtered, washed with cold methanol and recrystallized from ethanol-water (1.6 g, 91%); m.p. 262-264 °C; $[\alpha]_D$ -24°, $[\alpha]_{578}$ -24°, $[\alpha]_{546}$ -27°, $[\alpha]_{436}$ -33°, $[\alpha]_{365}$ -64°, (*c* 0.5, H_2O), [literature:[20] m.p. 260 °C, $[\alpha]_D$ -23°]; ν_{max} 3300-3400 (NH, OH) and 1650 cm^{-1} (C=O, amide); δ_H (DMSO-d_6) 8.36 (d, 1H, NH), 4.98 (d , OH), 4.92 (t , OH), 4.87 (m , 2OH), 4.69 (t , 1H, $J_{1,2}$= $J_{1,NH}$ = 9.1, H-1), 3.17 (m, H-2, H-3, H-5), 3.07 (m, 2H, H-2, H-4), 3.63 (dd, 1H, $J_{5,6}$ 5.4, H-6), 3.39 (dd, 1H, $J_{5,6}$ 5.4, $J_{6,6'}$ 11.5, H-6'), 1.84 (s, 3H, NCOMe); δ_H (D_2O) 4.91 (d, 1H, $J_{1,2}$ 9.1, H-1), 3.84 (dd, 1H, $J_{5,6}$ 2.1, H-6), 3.70 (dd, 1H, $J_{5,6}$ 5.2, $J_{6,6'}$ 12.3, H-6'), 3.51 (t, 1H, $J_{2,3} = J_{3,4}$=.9.2, H-3), 3.38 (t, 1H, H-2), 3.35 (t, 1H, $J_{4,5}$ 9.4, H-4), 2.03 (s, 3H, NCOMe); δ_C (DMSO-d_6) 169.8 (NCO), 79.5 (C-1), 78.5, 77.6, 72.5; 70.0 (C-2, C-3, C-4, C-5), 61.0 (C-6), 22.9 (NCOMe); δ_C (D_2O) 176.7 (NCO), 80.4 (C-1), 78.7 (C-5), 77.7 (C-3), 73.0 (C-4), 70.5 (C-2), 61.8 (C-6), 23.4 (NCOMe).

***N*-Acetyl-β-D-xylopyranosylamine (10).**[20] To a solution of **8** (1.0 g, 3.1 mmol) in methanol (5 mL) was added 1M sodium methoxide (0.3 mL), and the mixture was neutralized with Dowex 50W (H^+). The resulting solution was evaporated and the residue was crystallized from cold ethanol (0.4 g, 38%); m.p. 224-226 °C (dec.), $[\alpha]_D$ -1°, $[\alpha]_{578}$ -1°, $[\alpha]_{546}$ -1°, $[\alpha]_{436}$ +6°, $[\alpha]_{365}$ +25°, (*c* 0.5, H_2O), [literature:[20] 213-214

°C, $[\alpha]_D$ -1° (*c* 2, H_2O)]; ν_{max} 3400-3300 (NH, OH) and 1660 cm^{-1} (C=O, amide); δ_H (DMSO-d_6) 8.35 (d, 1H, NH), 5.02 (d, OH), 4.94 (d, OH), 4.89 (d, OH), 4.60 (t, 1H, $J_{1,2}$= $J_{1,NH}$ = 9.0, H-1), 3.62 (dd, 1H, $J_{4,5}$ 5.0, $J_{5,5'}$ 12.0, H-5), 3.23 (m, 1H, H-4), 3.12 (m, 1H, H-3), 3.03 (m, 2H, H-2, H-5), 1.83 (s, 3H, NCOMe); δ_H (DMSO-d_6 + D_2O) 4.57 (d, 1H, $J_{1,2}$ 9.0, H-1), 3.63 (dd, 1H, $J_{4,5}$ 5.0, $J_{5,5'}$ 12.0, H-5), 3.27 (m, 1H, $J_{4,5'}$ 3.6, H-4), 3.16 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.0, H-3), 3.05 (m, 2H, H-2, H-5), 1.83 (s, 3H, NCOMe); δ_H (C_5D_5N) 9.56 (d, 1H, NH), 7.28 (d, OH), 7.11 (d, OH), 6.92 (d, OH), 5.62, (t, 1H, $J_{1,2}$ = $J_{1,NH}$ = 9.0, H-1), 4.09 (dd, 1H, $J_{4,5}$ 3.2, $J_{5,5'}$ 11.2, H-5), 3.95 (m, 2H, H-4, H-5'), 3.83 (m, 1H, H-3), 3.56 (m, 1H, H-2), 1,83 (s, 3H, NCOMe); δ_C (DMSO-d_6) 170.2 (NCO), 80.5 (C-1), 77.8 (C-3), 72.5 (C-2), 69.9 (C-4), 67.6 (C-5), 23.1 (NCOMe); δ_C (C_5D_5N) 170.8 (NCO), 81.9 (C-1), 79.8, 74.3, 71.3 (C-3, C-2, C-4), 69.1 (C-5), 23.3 (NCOMe).

***N*-Methyl-D-glucopyranosylamine (12).**[19] To a 33% solution of methylamine in ethanol (25 mL) was added D-glucose (5.0 g, 27.8 mmol) and the reaction mixture was stirred at 0 °C until complete dissolution. After 24 h at that temperature, the crystalline solid was filtered and washed successively with cold ethanol and diethyl ether (2.6 g, 49%);. m.p. 79-81 °C ; $[\alpha]_D$ -11°, $[\alpha]_{578}$ -11°, $[\alpha]_{546}$ -13°, $[\alpha]_{436}$ -20°, $[\alpha]_{365}$ -28°, (*c* 0.5, H_2O, in equilibrium), [literature:[19] 74-76 °C; $[\alpha]_D$ +1° (*c* 3.7, 0.1 M aq. $MeNH_2$)]; ν_{max} 3300 (NH, OH), 2800 (Me) and 1500 cm^{-1} (NH); δ_H (DMSO-d_6) 4.82 (m, 2OH), 4,53 (bs, OH), 4,39 (bs, OH), 3.65 (dd, 1H, $J_{6,6'}$ 11.5, H-6), 3.58 (d, 1H, $J_{1,2}$ 8.5, H-1), 3.41 (bs, OH), 3.40 (dd, 1H, H-6'), 3.13 (t, 1H, $J_{3,4}$ 8.3, H-3), 3.02 (m, 2H, H-4, H-5), 2.87 (t, 1H, $J_{2,3}$ 8.7, H-2), 2.35 (s, 3H, NMe); δ_H (DMSO-d_6 + D_2O) 3.68 (dd, 1H, $J_{5,6}$ ~2, $J_{6,6'}$ 11.7, H-6), 3.62 (d, 1H, $J_{1,2}$ 8.5, H-1), 3.45 (dd, 1H, $J_{5,6'}$ 4.8, H-6'), 3.18 (t, 1H, $J_{3,4}$ 8.3, H-3), 3.06 (m, 2H, H-4, H-5), 2.92 (t, 1H, $J_{2,3}$ 8.8, H-2), 2.35 (s, 3H, NMe); δ_H (D_2O) 3.96 (d, 1H, $J_{1,2}$ 8.8, H-1), 3.94 (dd, 1H, $J_{5,6}$ 2.1, H-6), 3.75 (dd, 1H, $J_{5,6'}$ 5.4, $J_{6,6'}$ 12.4, H-6'), 3.51 (t, 1H, $J_{3,4}$ 8.7, H-3), 3.43 (m, 2H, H-4, H-5), 3.24 (t, 1H, $J_{2,3}$ 8.9, H-2), 2.48 (s, 3H, NMe); δ_C (DMSO-d_6) 92.1 (C-1), 77.8, 77.7, 73.6, 70.8 (C-2, C-3, C-4, C-5), 61.7 (C-6), 32.2 (NMe); δ_C (D_2O) 91.4 (C-1), 77.6 (2C), 73.6, 70.7 (C-2, C-3, C-4, C-5), 61.6 (C-6), 31.7 (NMe).

***N*-Methyl-D-xylopyranosylamine (13).**[19] Starting from D-xylose (5.0 g, 27.8 mmol) and following the above protocol for **12**, the title compound was obtained (5.0 g, 91%); m.p. 107-109 °C; $[\alpha]_D$ -36°, $[\alpha]_{578}$ -36°, $[\alpha]_{546}$ -41°, $[\alpha]_{436}$ -67°, $[\alpha]_{365}$ -99° (*c* 0.5, H_2O, in equilibrium), [literature:[19], m.p. 109-111 °C, $[\alpha]_D$ -30°, (*c* 3.3, 0.1 M aq. $MeNH_2$)]; ν_{max} 3300 (NH, OH), 2900 (Me) and 1680 cm^{-1} (NH); δ_H (DMSO-d_6) 4.88 (m , 2OH), 4.54 (bs, OH), 3.64 (dd, 1H, $J_{4,5}$ 5.2, $J_{5,5'}$ 11.0, H-5), 3.53 (d, 1H, $J_{1,2}$ 8.5, H-1), 3.23 (m, 2H, H-4, OH), 3.07 (t, 1H, $J_{3,4}$ 8.6, H-3), 2.96 (t, 1H, $J_{4,5'}$ 10.7, H-5'), 2.86 (t, 1H, $J_{2,3}$ 8.5, H-2), 2.32 (s, 3H, NMe); δ_H (D_2O) 3.96 (dd, 1H, $J_{4,5}$ 5.4, H-5), 3.92 (d, 1H, $J_{1,2}$ 8.9, H-1), 3.64 (m, 1H, H-4), 3.47 (t, 1H, $J_{3,4}$ 9.0, H-3), 3.33 (t, 1H, $J_{4,5'}$ 11.2, $J_{5,5'}$ 11.2, H-5'), 3.24 (t, 1H, $J_{2,3}$ 8.9, H-2), 2.47 (s, 3H, NMe); δ_C (DMSO-d_6) 92.7 (C-1), 77.2, 73.1, 69.9 (C-2, C-3, C-4), 66.6 (C-5), 31.9 (NMe); δ_C (D_2O) 92.3 (C-1), 77.5, 73.6, 70.2 (C-2, C-3, C-4), 67.0 (C-5), 31.6 (NMe).

X-Ray data of compound 1 .[23] A colorless prism with the dimensions 0.32 x 0.26 x 0.24 mm was used for data collection. The crystal system was determined to be monoclinic, space group $P2_1$, a = 5.427(1) Å, b = 8.010(1) Å, c = 21.454(1) Å, β = 92.19(1)°, V = 931.9(4) $Å^3$, Z = 2, δ(calcd) = 1.338 Mg m^{-3}, linear absorption coefficient μ = 0.114 mm^{-1}, and FW = 375.3 for $C_{15}H_{21}NO_{10}$, F(000) = 396. The total number of reflections was 4182, 3262 independent [R_i = 0.082], 1701 observed [$F > 4.0\sigma(F)$]. The number of refined parameters was 234. Final R = 0.054, wR = 0.068.

X-Ray data of compound 6.[23] A colorless prismatic crystal with the dimensions 0.40 x 0.25 x 0.24 mm was used for data collection. Crystal system: orthorhombic, space group: $P2_12_12_1$, a = 5.982(1) Å, b = 9.856(1) Å, c = 16.663(1) Å, V = 982.4(4) Å^3, Z = 4, δ(calcd) = 1.387 Mg m^{-3}, linear absorption coefficient μ = 0.115 mm^{-1}, and FW = 205.2 for $C_8H_{15}NO_5$, $F(000)$ = 440. The total number of reflections was 1827, 1664 independent [R_i = 0.021], 1613 observed [$F > 2.0\sigma(F)$]. The number of refined parameters was 127. Final R = 0.047, wR = 0.069.

X-Ray data of compound 8.[23] A colorless prismatic crystal with the dimensions 0.40 x 0.32 x 0.30 mm was used for data collection. Crystal system: orthorhombic, space group: $P2_12_12_1$, a = 8.085(1) Å, b = 9.676(1) Å, c = 21.310(2) Å, V = 1667.1(6) Å^3, Z = 4, δ(calcd) = 1.264 Mg m^{-3}, linear absorption coefficient μ = 0.106 mm^{-1}, and FW = 317.3 for $C_{13}H_{19}NO_8$, $F(000)$ = 672. The total number of reflections was 3533, 3321 independent [R_i = 0.011], 1750 observed [$F > 4.0\sigma(F)$]. The number of refined parameters was 199. Final R = 0.050, wR = 0.058.

X-ray data of compound 9.[23] A colorless prism with the dimensions 0.50 x 0.40 x 0.38 mm was used for data collection. Crystal system: orthorhombic, space group: $P2_12_12_1$, a = 7.862(1) Å, b = 9.425(1) Å, c = 14.029(1) Å, V = 1039.5(4) Å^3, Z = 4, δ(calcd) = 1.413 Mg m^{-3}, linear absorption coefficient μ = 0.122 mm^{-1}, and FW = 221.2 for $C_8H_{15}NO_6$, $F(000)$ = 472. The total number of reflections was 2317, 2144 independent [R_i = 0.025], 2065 observed [$F > 2.0\sigma(F)$]. The number of refined parameters was 136. Final R = 0.039, wR = 0.053.

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