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Note

Conformational preferences in glycosylamines. Implications for the exo-anomeric effect

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This work is dedicated, with respect and affection, to the memory of R.U. Lemieux

Abstract

The conformational preferences about the C–N bond in *N*-(4-methoxyphenyl)-2,3,4,6-tetra-*O*-acetyl-α (**1**) and β-D-glucopyranosylamine (**2**), in the solid state and in solution, have been investigated. The crystal structure of the axially substituted α anomer (**1**) indicates a conformational preference about the C-1–N bond in which $n_N \rightarrow \sigma^*_{C-O}$ exo-anomeric interactions may be expressed, although this conformational preference is not displayed in solution. The solution conformation relieves steric interactions that result from expression of the exo-anomeric effect in the solid-state conformation. The conformational preference in the equatorially substituted β anomer (**2**) both in solution and in the solid state is similar and permits expression of $n_N \rightarrow \sigma^*_{C-O}$ exo-anomeric interactions. The structural data for **1** and **2** indicate significant differences in O-5–C-1–N-1 bond angles but insignificant differences in each of the O-5–C-1 or C-1–N-1 bond lengths. The $J_{C\text{-}1\text{–}H\text{-}1}$ coupling constants in **1** and **2** indicate a greater coupling constant for the α anomer that is consistent with a dominant $n_O \rightarrow \sigma^*_{C-H}$ orbital interaction in the β anomer that weakens the C-1–H-1 bond.

Keywords: Glycosylamines; Conformational analysis; Solution and solid-state conformations; exo-Anomeric effect

1. Introduction

The anomalous axial preference of electronegative substituents at the anomeric center of the pyranose ring was first noted by Edward[1] and was clearly defined as the anomeric effect by Lemieux and Chü.[2] Since that time, the anomeric effect has been shown to be a general effect operating in X–A–Y fragments[3] and has been classified further in terms of the endo-anomeric effect[4] and the exo-anomeric effect.[5] The endo-anomeric effect refers to the preference of electronegative groups attached to the anomeric carbon for the axial orientation and has been rationalized in terms of stabilizing $n_X \rightarrow \sigma^*_{C-Y}$ orbital inter

Fig. 1. Stabilizing orbital interactions associated with the (a) endo-anomeric effect and (b), (c) exo-anomeric effect.

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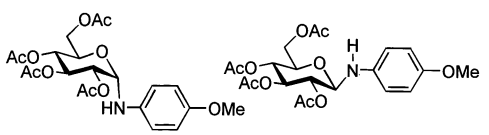
actions (Fig. 1(a)).[6] The exo-anomeric effect is the preference for the gauche conformation around the C-1 aglyconic carbon bond of glycopyranosides that has been rationalized in terms of $n_Y \rightarrow \sigma^*_{C-X}$ stabilizing orbital interactions (Fig. 1(b) and (c)).[6]

The reverse anomeric effect (RAE) was defined by Lemieux and Morgan[7] as the tendency of quaternary nitrogen aromatic systems such as pyridinium and imidazolium to adopt the equatorial orientation. Over the years, this topic has been studied extensively,[8–12] and recent evidence suggests that the equatorial preference results from non bonded repulsion in the axial isomer.[11g] The RAE has also been identified in systems with neutral and protonated amino and alkylamino substituents,[10] but this too has been accounted for in terms of steric effects.[6,11a,c,d,13] We have previously argued that the steric interactions in the axial isomers would be accentuated if the orientation about the C-2–N bond in 2-alkylaminoheterocyclohexanes were such that the $n_X \rightarrow \sigma^*_{C-Y}$ orbital interactions associated with the exo-anomeric effect were operative (Fig. 1(b), $Y = NR_1R_2$), thereby favoring the equatorial isomer.[6] We have also presented arguments in terms of $n_N \rightarrow \sigma^*_{C-O}$ or $n_N \rightarrow \sigma^*_{C-S}$ orbital interactions in *N*-arylglucopyranosylamines and *N*-aryl-5-thio-glucopyranosylamines, respectively (Fig. 1, $Y = NR_1R_2$; X = O, S) to account for differences in $J_{C\text{-}1\text{–}H\text{-}1}$ coupling constants.[13] However, experimental proof of the conformational preferences about the C(anomeric)–N bond was lacking. We chose to investigate such conformational preferences about the C-1–N bond in an anomeric pair of *N*-arylglucopyranosylamines **1** and **2**, and we report here data in the solid state and in solution to probe the role of exo-anomeric interactions.



1 **2**

The orbital interactions of possible relevance in a discussion of conformational effects operating in compounds **1** and **2** are shown in Fig. 2. The $n_O \rightarrow \sigma^*_{C-N}$ orbital interaction associated with the endo-anomeric effect in **1** is shown in Fig. 2(a) while the $n_N \rightarrow \sigma^*_{C-O}$ orbital interactions associated with the exo-anomeric effect in **1** and **2** are shown in Fig. 2(b) and (d), respectively. An alternative conformation about the C–N bond in **1**, which permits an endo-anomeric effect but not an exo-anomeric effect, is shown in Fig. 2(c). Finally, Fig. 2(e) shows an $n_O \rightarrow \sigma^*_{C-H}$ orbital interaction, which will be of importance in the later discussion of J_{C-H} values.

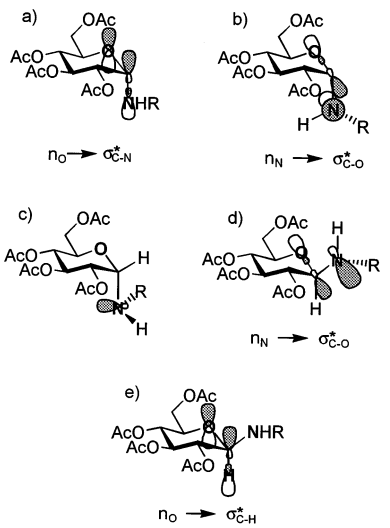


Fig. 2. Orbital interactions in the different conformations of axially and equatorially substituted glucopyranosylamines.

The crystal structure of compound **1** is shown in Fig. 3. The conformational preference about the C-1–N bond is such that the torsion angle C-11–N-1–C-1–C-2 is $-176.9(2)°$ (see Table 1), in agreement with the expression of an $n_N \rightarrow \sigma^*_{C-O}$ orbital interaction associated with the exo-anomeric effect (see Fig. 2(b)). This conformation necessarily points the hydrogen atom on nitrogen under the pyranose ring, giving an accentuated steric effect, as we had claimed earlier.[6] The conformational preference in solution is, however, different. Examination of $^3J_{H-H}$ coupling constant data[13] indicates that $^3J_{NH-H-1} = 2.5$ Hz, consistent with the presence of a gauche relationship between NH and H-1, as in Fig. 2(c), but not an anti relationship, as in Fig. 2(b). The unfavorable steric interaction observed in the solid-state structure is thus relieved in solution. Presumably, the conformational preference in the solid state results from crystal packing forces. It is noteworthy that ab initio calculations of axially substituted 2-

methylaminotetrahydropyran predict a conformation that resembles that shown in Fig. 2(c); that is, one that does not exhibit exo-anomeric interactions.[14]

The solid-state conformation in compound **2** is shown in Fig. 4. Once again, the conformation about the C–N bond permits expression of the $n_N \rightarrow \sigma^*_{C-O}$ exo-anomeric interaction. In this case, the conformational preference in solution is similar to that in the solid state since $^3J_{NH-H1} = 9.7$ Hz,[13] consistent with the presence of an anti relationship between NH and H-1, as shown in Fig. 2(d). The preference also corresponds to that of equatorially substituted 2-methylaminotetrahydropyran, predicted by ab initio calculations.[14]

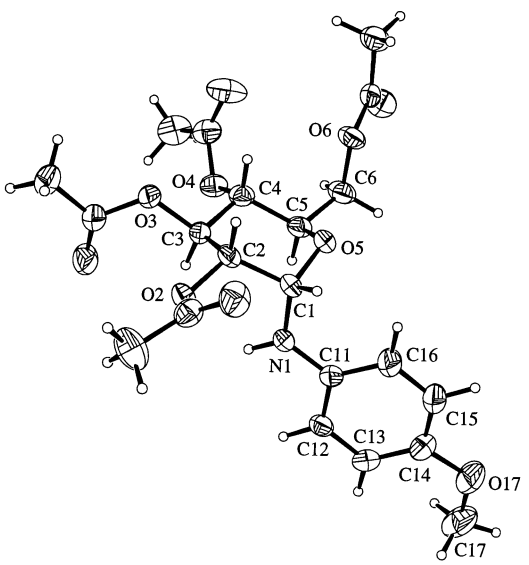


Fig. 3. The molecular structure of **1**. 50% Probability displacement ellipsoids are shown for non-hydrogen atoms. Hydrogen atoms are shown as spheres of arbitrary radius.

Table 1
Selected structural data for compounds **1** and **2**

	Compound **1**	Compound **2**
Torsion angles (°)		
O-5–C-1–N-1–C-11	62.5(3) [a]	−61.6(2)
C-2–C-1–N-1–C-11	−176.9(2)	−179.2(3)
N-1–C-1–O-5–C-5	59.4(2)	173.5(3)
Bond angles (°)		
O-5–C-1–N-1	114.3(2)	109.4(2)
C-1–N-1–C-11	122.7(2)	122.5(2)
C-1–O-5–C-5	114.2(1)	112.4(2)
C-2–C-1–N-1	111.8(2)	110.6(2)
Bond lengths (Å)		
O-5–C-1	1.449(3)	1.441(3)
C-1–N-1	1.418(3)	1.412(3)
O-5–C-5	1.422(3)	1.429(3)

[a] The numbers in parentheses indicate the standard deviation in the last digit.

It is of interest to compare the bond angles and bond lengths in the O–C–N acetal fragments in **1** and **2**. The O–C–N bond angle in the axially substituted compound **1** is greater than that in the equatorially substituted compound **2**, in agreement with previous studies of bond angle variations in acetals.[15] Surprisingly, however, the O-5–C-1 or C-1–N-1 bond lengths in the two isomers were the same within experimental error. One might have predicted that a dominant $n_N \rightarrow \sigma^*_{C-O}$ exo-anomeric interaction in compound **2** would have led to a shorter C–N bond and a longer C–O bond than those in compound **1**, in which the exo-anomeric interaction is opposed by an $n_O \rightarrow \sigma^*_{C-N}$ endo-anomeric interaction. The expected trends described here have certainly been observed in truncated model systems[10b,16] or in 2-methylaminotetrahydropyran,[14] predicted by ab initio calculations.

As a final point of interest, we comment on the $J_{C-1-H-1}$ coupling constants. It has been shown previously that these coupling constants are directly related to the magnitude of C–H bond strengths[17] and can be correlated with the operation of different orbital interactions.[13,17,18] The $J_{C-1-H-1}$ coupling constant in compound **1** is 166 Hz, while that in **2** is 154 Hz. This is the normal trend observed in pyranosides containing oxygen as the ring atom[17] and may be rationalized in terms of a dominant $n_O \rightarrow \sigma^*_{C-H}$ orbital interaction (see Fig. 2(e)) in the equatorially substituted compound **2**, which leads to a weakening of the C-1–H-1 bond. A corresponding interaction that would lead to a weakening of the C-1–H-1 bond in the axially substituted compound **1** might have been an $n_N \rightarrow \sigma^*_{C-H}$ orbital interaction in a conformation in which the lone pair orbital on nitrogen would be antiperiplanar to the C-1–H-1 bond. This interaction is analogous to that giving rise to the Bohlmann bands in the infrared spectra of quinolizidine alkaloids or of other amines, in which a lone

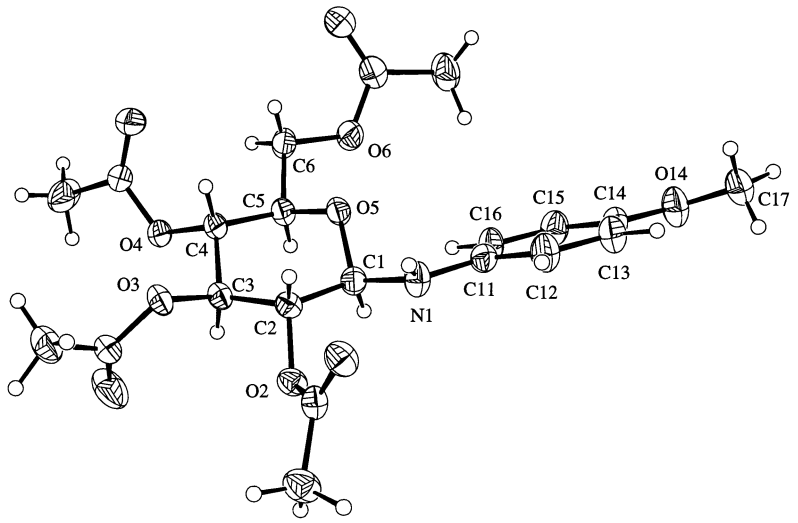


Fig. 4. The molecular structure of **2**. 50% Probability displacement ellipsoids are shown for non-hydrogen atoms. Hydrogen atoms are shown as spheres of arbitrary radius.

pair on nitrogen that is antiperiplanar to a C–H bond leads to a lower frequency C–H vibration.[19] However, the conformations populated in solution resemble that shown in Fig. 2(c) in which this interaction is not present. It is worthy of comment that the $J_{C\text{-}1\text{–}H\text{-}1}$ coupling constants in the anomeric pair of the corresponding *N*-aryl-5-thioglucopyranosylamines[13] exhibit the opposite trend, i.e., the axially substituted compound shows the smaller coupling constant. We rationalize this trend in terms of a lesser $n_s \rightarrow \sigma^*_{C\text{–}H}$ orbital interaction in the equatorial isomer, as compared to its oxygen congener, and a greater $n_N \rightarrow \sigma^*_{C\text{–}S}$ exo-anomeric interaction in this isomer that leads to greater *s*-character in the C–H bond. This latter effect outweighs the opposing, weak bond-lengthening effect in the equatorial isomer and leads to a reversal in the order of C-1–H-1 strengths. That the $n_s \rightarrow \sigma^*_{C\text{–}H}$ orbital interaction is not dominant in 1,3-dithiane and that there is a reversal in the order of axial versus equatorial bond strengths, relative to 1,3-dioxane, has already been demonstrated.[17a]

2. Experimental

The syntheses and characterization of compounds **1** and **2** have been described previously.[13] Crystallographic data for compound **1**: $C_{21}H_{27}NO_{10}$; colorless needles, $f_w = 453.44$, orthorhombic, $P2_12_12_1$, $Z = 4$, $a = 5.4553(3)$, $b = 18.724(1)$, $c = 22.5661(8)$ Å, $T = -100$ °C, $R = 0.028$ (calculated on F, $I > 3.00\sigma(I)$), GOF = 0.72. The data were collected on a Rigaku/ADSC CCD area detector in two sets of scans ($\varphi = 0.0$–$190.0°$, $\chi = -90°$; and $\omega = -19.0$ to 23.0, $\chi = -90°$), using 0.50° oscillations with 58.0-s exposures. The crystal-to-detector distance was 40.50 mm with a detector swing angle of −5.53°. The structure was solved by direct methods[20] and expanded using Fourier techniques.[21] The non-hydrogen atoms were refined anisotropically while all hydrogen atoms were refined isotropically. All other hydrogens were included in calculated positions. The absolute configuration was known from the synthetic method and was assigned accordingly. All calculations were performed using the TEXSAN[22] crystallographic software package of Molecular Structure Corporation.

Crystallographic data for compound **2**: $C_{21}H_{27}NO_{10}$; colorless parallelepiped; $f_w = 454.44$; monoclinic, space group $P2_1$; $Z = 2$; $a = 5.472(2)$, $b = 16.444(2)$, $c = 12.417(3)$ Å; $\beta = 94.84(3)°$; $T = 195$ K; $R_F = 0.027$ ($I_o > 2.50\sigma(I)$); GOF = 1.36. The data were collected on an Enraf–Nonius CAD4F diffractometer equipped with an in-house modified low temperature attachment and using graphite monochromatized Mo K_α radiation. The programs used for data collection,

absorption corrections, data reduction, direct methods structure solution, and graphical output were from the NRCVAX Crystal Structure System.[23] The structure was refined using CRYSTALS.[24]

Coordinates and anisotropic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms were initially placed in calculated positions. For each of the acetyl methyl groups, two complementarily staggered sets of rotationally disordered hydrogen atom sites were used, and their relative occupancy was refined. Group refinement was employed for all methyl groups, subject to soft restraints restricting each to near axial symmetry about the respective C–C or O–C bond. The coordinates of the hydrogen atom bonded to nitrogen were refined independently. For the remaining hydrogen atoms, coordinate shifts were linked with those of their respective carbon atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respectively bound atoms. Subsequently, the isotropic thermal parameters for appropriate groups of hydrogen atoms were constrained to have identical shifts during refinement. The absolute configuration was known from the synthetic method and was assigned accordingly.

3. Supplementary material

Full crystallographic details, excluding structural features, have been deposited with the Cambridge Crystallographic Data Centre (CCDC 153084 and 153048). Copies of these data may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http:\\www.ccdc.cam.ac.uk).

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