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Anomeric Effect of the Nitrogen Atom in the Isocyano and Urea Groups

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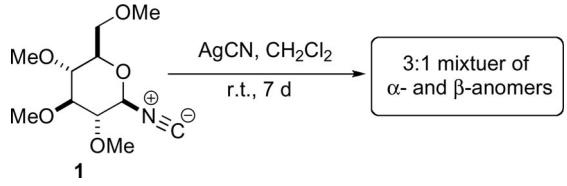
The anomeric effect associated with the nitrogen atom in the isocyano group was investigated by using ^{1}H NMR spectroscopic analysis of an anomeric pair of xylopyranosyl isocyanides **8** and **7**. We found that β-anomer **7** prefers to exist in the $^1C_4$ conformation in which the nitrogen atom in the isocyano group adopts an axial orientation. This observation, coupled with the results of X-ray crystallographic analysis establishes that the nitrogen atom in the isocyano group displays the anomeric effect. Furthermore, xylopyranosyl isocyanides **8** and **7** were transformed into the corresponding xylopyranosyl ureas **10** and **11**. In the case of the urea group, a normal sterically determined preference is observed in which the bulky urea substituents at the pyranose anomeric position occupy the equatorial position.

Introduction

The anomeric effect defines the preference for the axial orientation of electronegative substituents at C-1 of a pyranose ring, which is in marked contrast to expectations based on the sterically driven preference for equatorial cyclohexane conformers.[1] Elements in the first row of the periodic table show the anomeric effect, which diminishes with decreasing electronegativity (F > O > N > C).[2] In the case of nitrogen, the axial preference depends on the substituents at the nitrogen center. Horton reported the result of a comprehensive ^{1}H NMR spectroscopic investigation of pentopyranose derivatives,[3] which were used to analyze the anomeric effect of N-substituted glycosylamines by Paulsen.[4] The ^{1}H NMR spectroscopic measurements of the conformational equilibrium for N-substituted *N*-pentopyranosylamines show that the order of axial preference is as follows: $NPPh_3$ > OAc> N_3 > $NHCOCF_3$ > NHCOAr > NH_2 = NHAc. The anomeric effect is largest for more electronegative sp- and sp^2-hybridized nitrogen groups, whereas substituents such as NH_2 and NHAc show the usual sterically driven preference for the equatorial dispositions.

Although several nitrogen-containing groups exhibit the anomeric effect, the isocyano groups have not been the subject of definitive efforts. Descotes described a study of the anomeric equilibration of glucopyranosyl isocyanide in the presence of silver cyanide (Scheme 1),[5] which show that starting from pure β-anomer **1** an equilibrium is reached after 7 days via an isocyanide–silver complex. This finding appears to suffer from the drawback that the isocyanide–silver complex present in the equilibrium mixture is neglected and that detailed experimental procedures were not described.



Scheme 1. Anomerization of glucopyranosyl isocyanide.

In recent years, glycosyl isocyanides have played an increasing role in organic synthesis; for example, oxidation of glycosyl isocyanides generates highly reactive glycosyl isocyanates, which have been used for the synthesis of glycoconjugates.[6] Danishefsky reported a reaction of isocyanides with carboxylic acids and expand its chemistry for the synthesis of asparagine-linked *N*-glycosyl amino acids starting from glycosyl isocyanides.[7] In order to develop the chemistry of glycosyl isocyanides further, knowledge about the anomeric effect of the nitrogen atom in the isocyano group is required so that conformational behavior and reactivity can be predicted. In this context, we have undertaken a ^{1}H NMR spectroscopic study of pentopyranosyl isocyanides to reveal the anomeric effect of the nitrogen atom in the isocyano group.

Horton reported an impressive ^{1}H NMR spectroscopic analysis of tri-*O*-acetyl-β-D-xylopyranosyl chloride (**2**) in $CDCl_3$ solution, which showed that **2** existed preferentially in the $^1C_4$ conformation, having the chlorine atom axially oriented even though all the acetyl substituents in this conformation are in axial positions (Scheme 2).[8]

This unusual conformational behavior of the xylose derivative is considered to be the manifestation of the anomeric effect of chlorine, which exceeds the steric destabilizing influence of four axial groups and two *syn*-diaxial interac-

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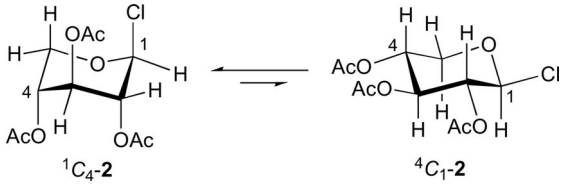
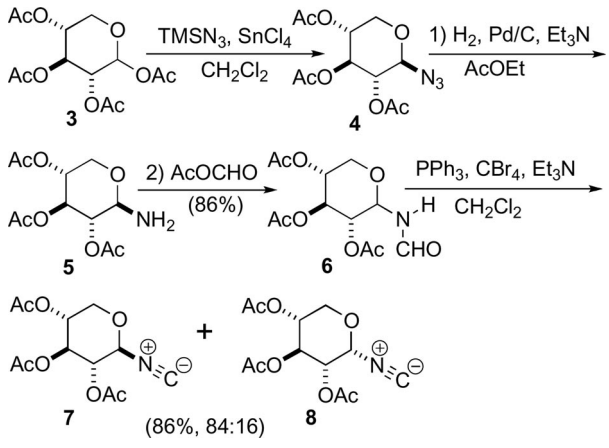


Scheme 2. Conformational equilibrium of tri-*O*-acetyl-β-D-xylopyranosyl chloride.

tions. Based on this precedent, we selected the β-isocyanide of xylose to examine the anomeric effect of the nitrogen atom in the isocyano group by using ^{1}H NMR spectroscopy.

Results and Discussion

We initially planned to synthesize β-xylopyranosyl isocyanide **7** starting from β-azide **4**, which was prepared by the procedure reported earlier by Paulsen[9] (Scheme 3). Treatment of acetyl xylose **3** with trimethylsilyl azide in the presence of stannous chloride gave β-azide **4** exclusively. Catalytic hydrogenation of the azide in **4** gave glycosylamine **5**, which was immediately subjected to acetic formic anhydride to avoid hydrolysis of the labile glycosylamine. Dehydration of resulting formamide **6**, carried out by using our previously reported method,[10] produced β-isocyanide **7** as a crystalline substance (m.p. 115 °C). During repeated syntheses of β-isocyanide **7**, we were pleased to find that α-anomer **8** was also formed as a minor product, which presumably arose by isomerization of β-glycosylamine **5** during its preparation (**4** → **5**) and/or formylation (**5** → **6**) steps. Moreover, fortuitous α-isocyanide **8** was also found to be a crystalline compound (m.p. 103 °C). Contrary to the initial plan, we obtained an anomeric pair of xylopyranosyl isocyanides **7** and **8** after careful purification of a mixture of products (74% combined yield with a ratio of 84:16 from β-azide **4**). At this point, we decided to carry out both ^{1}H NMR spectroscopic and X-ray analyses of xylopyranosyl isocyanides **7** and **8** to gain insight into their structures and conformational behaviors.



Scheme 3. Unexpected synthesis of both anomers of xylopyranosyl isocyanides.

The ^{1}H NMR spectra of xylopyranosyl isocyanides **8** and **7** measured in $CDCl_3$ are shown in Figure 1,[11] and the chemical shift and coupling constant data are summarized in Tables 1 and 2. In the case of α-anomer **8**, the H-1 resonance appears at low field (δ = 5.50 ppm) as a doublet ($J_{1,2}$ = 4.6 Hz), indicating that H-1 and H-2 are gauche-disposed. The H-2 resonance at δ = 4.87 ppm appears as a doublet of doublets with a large (9.6 Hz) coupling to H-3, which is in accord with a *trans*-diaxial arrangement of H-2 and H-3. The H-3 signal appearing at δ = 5.46 ppm splits as a triplet through large (9.6 Hz) coupling with H-2 and H-4, in accord with the *trans*-diaxial arrangement of H-2, H-3, and H-4. The H-4 signal is observed at δ = 4.99 ppm as a doublet of doublets of doublets ($J_{4,5'}$ = 10.7 Hz, $J_{3,4}$ = 9.6 Hz, $J_{4,5}$ = 5.9 Hz), showing that H-4 and H-5′ are axially disposed. These NMR spectroscopic data are fully consistent with the assignment of α-isocyanide **8** to the $^4C_1$ conformation.

Surprisingly, β-isocyanide **7** has a remarkably different ^{1}H NMR spectrum from that of the α-anomer. Two doublets of doublets in the spectrum of **7** appearing at δ = 3.70 and 4.29 ppm are assigned to the protons on C-5. A geminal coupling of $J_{5,5'}$ = 12.9 Hz and small coupling constants of $J_{4,5'}$ = 5.4 Hz and $J_{4,5}$ = 3.4 Hz indicate that H-4 and both H-5 and H-5′ have a gauche relationship. In addition, the H-3 resonance appears at δ = 5.08 ppm as a triplet with $J_{2,3}$ = $J_{3,4}$ = 5.4 Hz. The doublet at δ = 5.03 ppm is assigned to H-1, which has $J_{1,2}$ = 4.6 Hz, indicating a *trans*-diequatorial relationship between H-1 and H-2. It is concluded from the results of the NMR spectroscopic investigation that the nitrogen atom in the isocyano group at C-1 is axially oriented and that β-anomer **7** adopts the $^1C_4$ conformation preferentially.

Durette and Horton described the conformational equilibrium of some peracetylated aldopentopyranosyl halides in $CDCl_3$ solution.[8] In their studies, the proportions of the $^4C_1$ to $^1C_4$ conformers present at equilibrium were calculated by using the time-averaged coupling constants $J_{4,5}$ and $J_{4,5'}$. The $J_{4,5a}$ value of 12.1 Hz for the tri-*O*-acetyl-α-D-xylopyranosyl chloride was taken as the limiting magnitude of $J_{4,5a}$. The model compound chosen for the lower limit of the smaller $J_{4e,5e}$ was tri-*O*-acetyl-β-D-arabinopyranosyl bromide, and the value of 1.5 Hz was used as the limiting magnitude of $J_{4e,5e}$. With these values and the Winstein–Holness equation in mind,[12] the conformational populations of the $^1C_4$ and $^4C_1$ conformers of glycopyranosyl isocyanides were calculated by the observed time-averaged values of $J_{4,5}$ and $J_{4,5'}$, giving the values of $K = {}^4C_1/{}^1C_4$ = 6.6 for α-isocyanide **8** and that of 0.58 for β-anomer **7** (Table 3). Consequently, the results of this ^{1}H NMR spectroscopic study demonstrate the preferential axial disposition of the nitrogen atom in the isocyano group at the pyranose C-1, which is a manifestation of an anomeric effect of the nitrogen atom in the isocyano group.

The molecular geometry variation associated with the anomeric effect has been well recognized not only in the preference of gauche conformations about RO–CX bonds but also in the characteristic patterns of bond lengths and

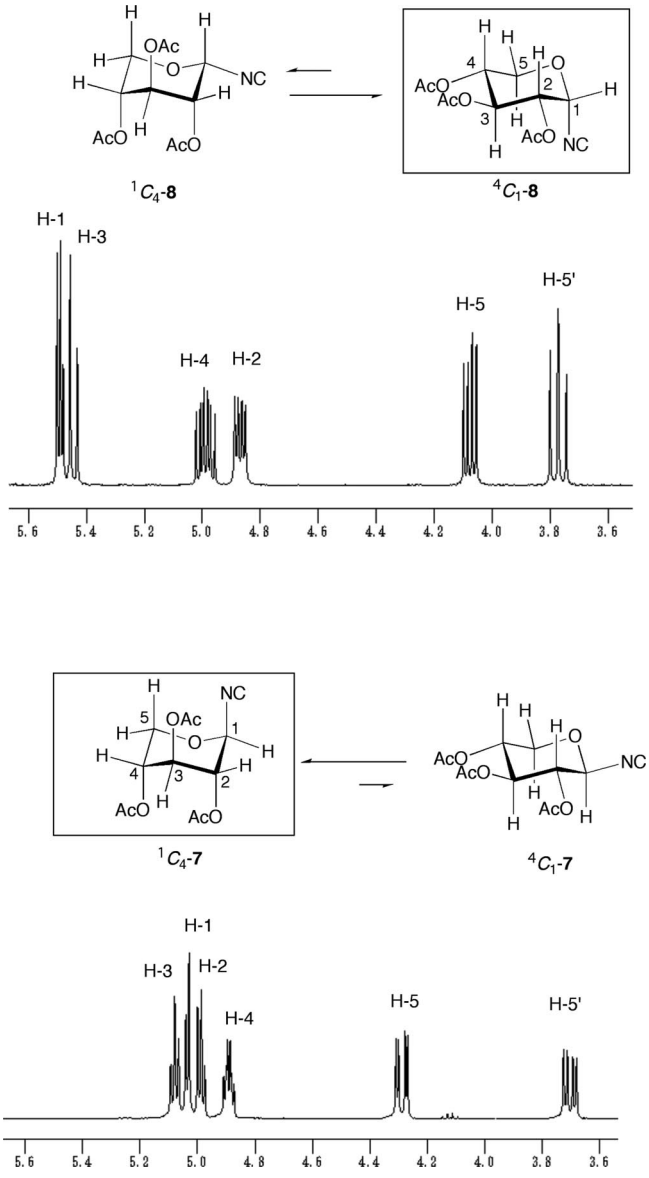


Figure 1. ^{1}H NMR spectra (400 MHz), signal assignments (the proton on C-5 giving high-field signals is designated H-5′), and conformational equilibrium of α- and β-isocyanides in $CDCl_3$.

Table 1. Selected ^{1}H NMR chemical shifts (δ)[a] in isocyanides **8** and **7** in $CDCl_3$.

	H-1	H-2	H-3	H-4[c]	H-5	H-5′
α-Isocyanide **8**	5.50	4.87	5.46	4.99	4.08	3.77
β-Isocyanide **7**	5.03	4.99	5.08	4.89	4.29	3.70

[a] In ppm relative TMS at 23 °C.

Table 2. Selected ^{1}H NMR spin coupling constants (J)[a] in isocyanides **8** and **7** in $CDCl_3$.

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
α-Isocyanide **8**	4.6	9.6	9.6	5.9	10.7	11.7
β-Isocyanide **7**	4.6	5.4	5.4	3.4	5.4	12.9

[a] In Hz.

Table 3. Conformational equilibrium of isocyanides **8** and **7** in $CDCl_3$ at 23 °C.

	$^4C_1$ [%]	$^1C_4$ [%]	$K = {}^4C_1/{}^1C_4$
α-Isocyanide **8**	87	13	6.6
β-Isocyanide **7**	37	63	0.58

angles associated with particular conformations. Altona and Havinga reported the crystallographic data for bond lengths in *cis* and *trans*-2,3-dichloro-1,4-dioxanes and suggested that the shortening and lengthening of the C–O and C–Cl bonds result from charge delocalization when an unshared pair of electrons is in antiperiplanar orientation to a polar bond.[13] Jeffrey and his associates carried out ab initio molecular orbital calculations that reproduce the crystallographic data of bond lengths and angles around the anomeric centers in pyranoses and pyranosides.[14]

In order to gain more insight into the anomeric effect of the nitrogen atom in the isocyano group, X-ray crystallographic analysis of the xylopyranosyl isocyanides were carried out. Colorless prismatic crystals of α-isocyanide **8** were found to be space group of $P2_1$ (#4) with parameters refined to an R value of 5.7%. α-Anomer **8** is present as four conformers in the asymmetric cell, one of which is depicted in Figure 2. In the crystalline state, α-isocyanide **8** adopts a $^4C_1$ conformation, which is identical to that observed in solution. On the other hand, the space group of a prismatic orthorhombic crystal of β-isocyanide **7** is determined to be $P2_12_12_1$ (#19) with an R value of 4.4%. Contrary to our expectation, β-anomer **7** exits in a $^4C_1$ conformation, which contrasts the preferred $^1C_4$ conformation in solution.[15]

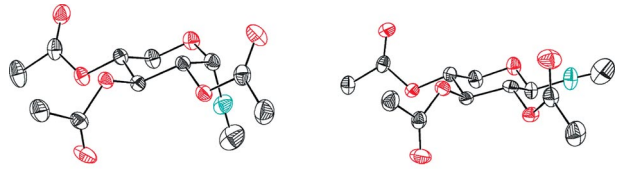


Figure 2. ORTEP plot of α- and β-isocyanides **8** and **7**. Hydrogen atoms are omitted for clarity.

The crystal structures of xylopyranosyl isocyanides **8** and **7** offer an appropriate opportunity to analyze the anomeric effect of the nitrogen atom in the isocyano group owing to the fact that both anomers have similar $^4C_1$ conformation. The ring oxygen of the α-isocyanide **8** contains an unshared pair of electrons, which is oriented antiperiplanar to a polar C1–N bond. This disposition is ideal for delocalization of the oxygen lone pair of electrons toward the electron-deficient anomeric carbon (Figure 3). As a result, the lengthening of the C1–N bond of α-isocyanide **8** is expected in comparison with that of β-anomer **7**, which contains an equatorial isocyano group. In addition, charge delocalization must bring double-bond character to the O5–C1 bond, which should tend to render the atoms involved somewhat trigonal in character. This would be manifested in valence bond angles that are greater than the normal 109.5° tetrahedral angle.

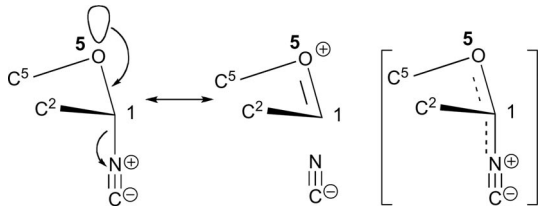


Figure 3. Double-bond–no-bond resonance structures of α-isocyanide **8**.

The crystallographically determined bond lengths and angles relevant to the anomeric effect are listed in Tables 4 and 5. While a difference of the O5–C1 bond length between two anomers is not evident, the distance between C-1 and the nitrogen atom in the α-isocyanide (1.428–1.407 Å) is substantially longer than that of the β-anomer (1.396 Å). Further subtle differences also exist in the valence angles associated with the anomeric center. While the C5–O5–C1 valence bond angle in the β-anomer (109.1°) is near the tetrahedral angle of 109.5°, the corresponding C5–O5–C1 bond angle in the α-anomer is considerably greater (114.3–111.9°). In addition, the O5–C1–N angle of the α-isocyanide (112.2–110.9°) compared with that of the β-anomer (106.7°) shows that the anomeric C-1 carbon of the α-isocyanide is somewhat trigonal in character.[16] Representative bond lengths and angles are depicted in Figure 4. Some bond lengths and angles around the anomeric centers in the α- and β-isocyanides are in accord with expectations based on electron delocalization.

Table 4. Valence bond lengths [Å] around the anomeric C-1 carbon atoms.

	O5–C1	C1–N
α-Isocyanide **8**	1.425–1.391	1.428–1.407
β-Isocyanide **7**	1.403	1.396

Table 5. Bond angles [°] around the anomeric C-1 carbon atoms.

	C5–O5–C1	O5–C1–N	O5–C1–C2	C2–C1–N
α-Isocyanide **8**	114.3–111.9	112.2–110.9	111.5–109.1	110.8–109.0
β-Isocyanide **7**	109.1	106.7	110.6	108.7

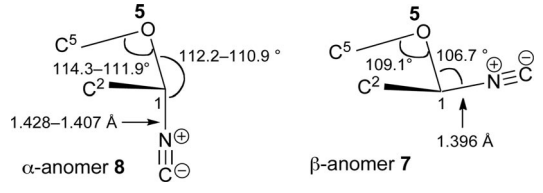
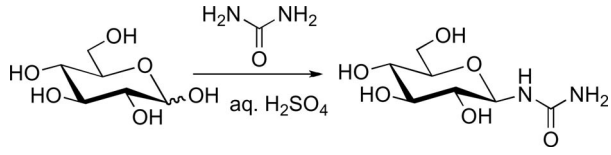


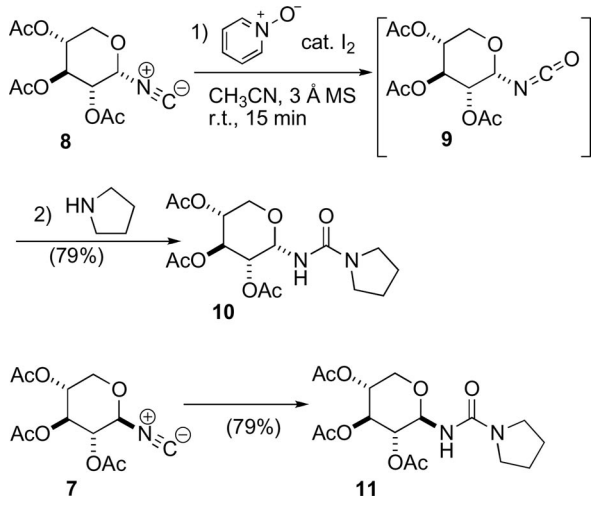
Figure 4. Selected bond lengths and valence bond angles associated with the anomeric C-1 carbon atoms.

The acid-catalyzed condensation of D-glucose with urea in water was reported to produce the β-urea glycoside predominantly (Scheme 4).[17] Although this reaction shows that the thermodynamically controlled reaction conditions lead to the stable β-anomer, no other studies have been designed to examine the anomeric effect of the urea group. In this context, isocyanides **8** and **7** were transformed into the corresponding ureas to evaluate the anomeric effect of the urea group by ^{1}H NMR spectroscopic analysis. Actually, we have already established a transformation of glycopyranosyl isocyanides into the corresponding glycopyranosyl ureas, which proceeds with retention of configuration at the anomeric positions.[6]



Scheme 4. Acid-catalyzed condensation of D-glucose with urea in water.

The routes for the synthesis of xylopyranosyl ureas **10** and **11** starting from the respective isocyanide **8** and **7** are shown in Scheme 5. An acetonitrile solution of α-isocyanide **8** and pyridine *N*-oxide in the presence of powdered 3 Å molecular sieves was treated with a catalytic amount of iodine. The oxidation reaction of the isocyano group in **8** was complete at room temperature after 15 min and generated xylopyranosyl isocyanate **9**. Subsequent treatment of the resulting reaction mixture with pyrrolidine converted in situ generated isocyanate **9** into stable urea **10**.[18] After workup, α-xylopyranosyl urea **10** was isolated in 79% yield. Using the same method, β-urea **11** was obtained starting from β-isocyanide **7** in 79% overall yield.



Scheme 5. Synthesis of xylopyranosyl ureas from isocyanides.

The ^{1}H NMR spectra of α- and β-xylopyranosyl ureas **10** and **11** in $CDCl_3$ are shown in Figure 5. Deuterium exchange experiments of the NH group in urea by the addition of one drop of CD_3OD to the $CDCl_3$ solutions led to the assignment of the NH and H-1 signals.[19] Conclusive signal assignment of α-urea **10** could not be performed by 2D ^{1}H–^{1}H COSY owing to its small coupling constants. Accordingly, selective spin decoupling experiments of α-urea **10** were carried out to make full assignments, which led to the observation of W-coupling between H-3 and H-5′. ABX analysis of H-5 and H-5′ was carried out,[20] and

the resulting coupling constant and chemical shift values were confirmed by employing spin simulations.[21] The signal assignments of β-urea **11** were performed through 2D ^{1}H–^{1}H COSY analysis without problems. The selected chemical shift and coupling constant data for xylopyranosyl ureas **10** and **11** are collected in Tables 6 and 7.

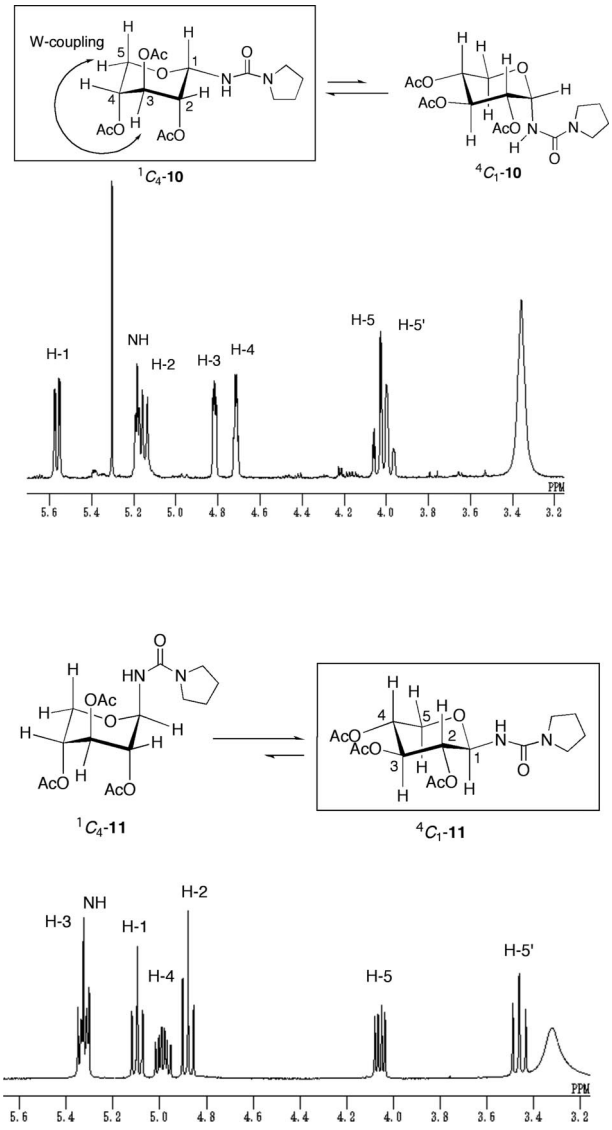


Figure 5. ^{1}H NMR spectra and signal assignments of **10** and **11** in $CDCl_3$.

Table 6. Selected ^{1}H NMR chemical shifts (δ)[a] in xylopyranosyl ureas **10** and **11** in $CDCl_3$.

	H-1	H-2	H-3	H-4	H-5	H-5′	H-5
α-Urea **10**	5.56	4.82	5.18	4.71	4.04	3.98	5.15
β-Urea **11**	5.10	4.88	5.33	4.99	4.06	3.46	5.32

[a] In ppm relative to TMS, 25 °C.

Inspection of these NMR spectroscopic data established that transformations of α-isocyanide **8** into α-urea **10** results in the $^4C_1$ to $^1C_4$ ring flip and that conversion of β-isocyanide **7** into β-urea **11** follows vice versa. Calculated equilibrium constants ($K = {}^4C_1/{}^1C_4$) for the α- and β-ureas are tabulated in Table 8. These observations clearly indicate that the urea group displays the usual steric preference for the equatorial disposition, which establishes that steric factors govern the conformational preference of glycosyl ureas.

Table 7. Selected ^{1}H NMR spin coupling constants (J)[a] in xylopyranosyl ureas **10** and **11** in $CDCl_3$.

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	$J_{1,NH}$	$J_{3,5'}$
α-Urea **10**	2.3	3.7	3.7	2.6	2.7	13.4	9.3	1.0
β-Urea **11**	9.5	9.5	9.5	10.7	5.6	11.7	9.3	–

[a] In Hz.

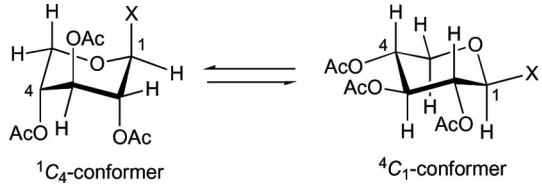
Table 8. Conformational equilibrium of ureas **10** and **11** in $CDCl_3$ at 25 °C.

	$^4C_1$ [%]	$^1C_4$ [%]	$K = {}^4C_1/{}^1C_4$
α-Urea **10**	12	88	0.12
β-Urea **11**	85	15	5.6

Conclusions

^{1}H NMR spectroscopic analysis of the anomeric pair of tri-*O*-acetyl-D-xylopyranosyl isocyanides **7** and **8** in $CDCl_3$ solution demonstrates the existence of an anomeric effect of the nitrogen atom in the isocyano group, which prefers to adopt an axial orientation at the C-1 positions of pyranoses. X-ray analysis of xylopyranosyl isocyanides **7** and **8** and comparison of bond lengths and bond angles around the anomeric positions also provides support for the anomeric effect of the nitrogen atom in the isocyano group. To estimate the magnitude of the anomeric effect of the nitrogen atom in the isocyano group, we collected and compared the equilibrium constant ($K = {}^4C_1/{}^1C_4$) of each tri-*O*-acetyl-β-D-xylopyranosyl chloride **2**,[8] acetate **3**,[22] azide **4**,[4] and isocyanide **7** (Table 9), which shows an order of axial preference in β-xylopyranosyl derivatives as follows: –Cl > –NC > –OAc > $–N_3$.

Table 9. Equilibrium constants ($K = {}^4C_1/{}^1C_4$) of tri-*O*-acetyl-β-D-xylopyranosyl derivatives.



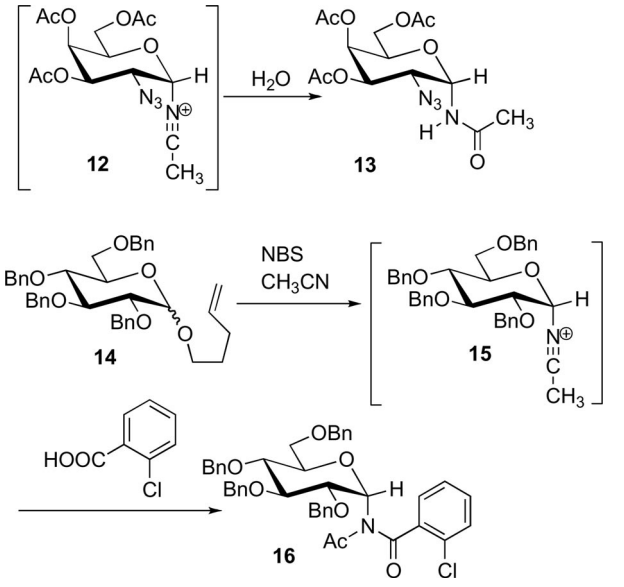
	2 (X = Cl)[a]	**3** (X = OAc)[b]	**4** (X = N_3)[c]	**7** (X = NC)
$K = {}^4C_1/{}^1C_4$	0.26	2.6	4.0	0.58

[a] Calculated by ^{1}H NMR spectroscopic analysis measured in $CDCl_3$ at 31 °C. [b] Calculated by ^{1}H NMR spectroscopic analysis measured in [D_6]acetone at 31 °C. [c] Calculated by ^{1}H NMR spectroscopic analysis measured in $CDCl_3$.

The anomeric effect of the urea group was evaluated by using ^{1}H NMR spectroscopic analysis of xylopyranosyl ureas **10** and **11**, which were generated from the corresponding xylopyranosyl isocyanides **8** and **7**. We found that

the urea substituent displays a usual steric preference for the equatorial orientation, which confirmed that the anomeric effect of urea is not observed as in the case of $–NH_2$ and –NHAc.

Finally, it is interesting to see if the anomeric effect of the nitrogen atom in the isocyano group is applied to hypothesized glycosyl α-acetonitrilium ion intermediates. In the study of azidonitration of tri-*O*-acetyl-D-galactal, Remieux isolated α-acetoamide **13** as a byproduct, which was postulated to be derived from α-acetonitrilium intermediate **12**[23] (Scheme 6). Fraser-Reid reported that oxidative hydrolysis of *n*-pentenyl glycoside **14** with NBS in wet acetonitrile provided α-*N*-acetyl glycopyranosylamine **16**.[24] The α-selectivity observed in this reaction was explained by invoking the intermediacy of α-acetonitrilium ion **15**.



Scheme 6. Probable intermediates of glycosyl acetonitrilium ions.

The reverse anomeric effect is known to operate in the form of an equatorial preference of positively charged electron-withdrawing substituents at anomeric positions of pyranoses. Accordingly, acetonitrilium glycosides, such as **12** and **15**, displaying a preference for an α-configuration at the anomeric positions are recognized as the counterexamples of the reverse anomeric effect.[25] The structural similarity between the isocyanide and acetonitrilium ions suggests that the α-configuration for the acetonitrilium glycosides should be stabilized by the anomeric effect.

Experimental Section

2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl Isocyanide (7) and 2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl Isocyanide (8): A solution of glycosyl azide **4** (500 mg, 1.66 mmol), triethylamine (0.70 mL, 5.0 mmol), and palladium on activated carbon (5%, 124 mg) in AcOEt (14.0 mL) was stirred vigorously under a hydrogen atmosphere for 2 h. The resultant mixture was treated with acetic formic anhydride (0.70 mL, 8.3 mmol). After being stirred at room temperature for 3 h, the reaction mixture was filtered through Super Cell and concentrated under reduced pressure. Purification by silica gel chromatography (AcOEt/hexane, 4:1) afforded a mixture of formamides **6** (434 mg, 86%) as a white solid. To a solution of formamides **6** (434 mg, 1.43 mmol), triethylamine (1.10 mL, 8.59 mmol), and triphenylphosphane (938 mg, 3.58 mmol) dissolved in CH_2Cl_2 (17 mL) cooled to –15 °C was added carbon tetrabromide (1.70 g, 5.01 mmol) portionwise. After stirring at 0 °C for 30 min, the cooling bath was removed. The reaction mixture was poured into aqueous NH_4Cl and then stirred at room temperature for 1 h. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resultant residue was subjected to silica gel chromatography (Et_2O/hexane, 4:1) to afford β-isocyanide **7** (237 mg, 58%), a mixture of β-isocyanide **7** and α-isocyanide **8** (ca. 70:30, 89 mg, 21%), and α-isocyanide **8** (30 mg, 7%) as a white solid. Data for β-isocyanide **7**: m.p. 115–116 °C (AcOEt/hexane). $[\alpha]_D^{21}$ = –87.6 (c = 1.01, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2149, 1763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, OAc), 2.13 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 3.70 (dd, J = 12.9, 5.4 Hz, 1 H, 5′-H), 4.29 (dd, J = 12.9, 3.4 Hz, 1 H, 5-H), 4.89 (td, J = 5.4, 3.4 Hz, 1 H, 4-H), 4.99 (br. t, J = 5.4, 4.6 Hz, 1 H, 2-H), 5.03 (d, J = 4.6 Hz, 1 H, 1-H), 5.08 (t, J = 5.4 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.50, 20.69, 62.19, 66.48, 67.58, 68.33, 78.46, 164.25, 168.94, 169.20, 169.54 ppm. $C_{12}H_{15}NO_7$ (285.08): calcd. C 50.53, H 5.30, N 4.91; found C 50.70, H 5.35, N 5.05. Data for α-isocyanide **8**: m.p. 103–104 °C (ether). $[\alpha]_D^{22}$ = +156.9 (c = 0.87, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2129, 1757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 6 H, 2 OAc), 2.14 (s, 3 H, OAc), 3.77 (br. t, J = 11.7, 10.7 Hz, 1 H, 5′-H), 4.08 (dd, J = 11.7, 5.9 Hz, 1 H, 5-H), 4.87 (dd, J = 9.6, 4.6 Hz, 1 H, 2-H), 4.99 (ddd, J = 10.7, 9.6, 5.9 Hz, 1 H, 4-H), 5.46 (t, J = 9.6 Hz, 1 H, 3-H), 5.50 (d, J = 4.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.45, 20.54, 61.33, 67.89, 68.67, 68.76, 78.81, 165.27, 169.49, 169.71, 169.78 ppm. $C_{12}H_{15}NO_7$ (285.08): calcd. C 50.53, H 5.30, N 4.91; found C 50.85, H 5.47, N 5.10.

2,3,4-Tri-*O*-acetyl-*N*-(pyrrolidinocarbonyl)-α-D-xylopyranosylamine (10): To a solution of α-xylopyranosyl isocyanide **9** (30 mg, 0.11 mmol), pyridine *N*-oxide (30 mg, 0.32 mmol), and powdered 3 Å molecular sieves (23 mg) in dichloromethane (2.80 mL) under an argon atmosphere was added iodine (2.0 mg, 0.0070 mmol). After stirring at room temperature for 15 min, pyrrolidine (0.026 mL, 0.32 mmol) was added. The resulting reaction mixture was stirred at room temperature for 30 min and then filtered. The filtrate was poured into saturated aqueous $NaHSO_3$ solution, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt) to afford α-urea **10** (31 mg, 79%) as an amorphous white solid. $[\alpha]_D^{22}$ = –19.8 (c = 1.01, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3364, 2975, 2957, 2876, 1755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.92 (br. s, 4 H, -NCH_2-CH_2-), 2.11 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 2.17 (s, 3 H, OAc), 3.36 (br. s, 4 H, -NCH_2-), 3.98 (ddd, J = 13.4, 2.7, 1.0 Hz, 1 H, 5′-H), 4.04 (dd, J = 13.4, 2.6 Hz, 1 H, 5-H), 4.71 (m, 1 H, 4-H), 4.82 (dd, J = 3.7, 2.3 Hz, 1 H, 2-H), 5.15 (d, J = 9.3 Hz, 1 H, NH), 5.18 (td, J = 3.7, 1.0 Hz, 1 H, 3-H), 5.56 (dd, J = 9.3, 2.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.64, 20.69, 20.80, 25.30, 45.43, 64.33, 66.32, 67.23, 68.86, 75.89, 154.61, 168.64, 169.45, 169.59 ppm. $C_{16}H_{24}N_2O_8$ (372.15): calcd. C 51.61, H 6.50, N 7.52; found C 51.97, H 6.76, N 7.44.

2,3,4-Tri-*O*-acetyl-*N*-(pyrrolidinocarbonyl)-β-D-xylopyranosylamine (11): To a solution of β-xylopyranosyl isocyanide **7** (30 mg, 0.11 mmol), pyridine *N*-oxide (30 mg, 0.32 mmol), and powdered 3 Å molecular sieves (23 mg) in dichloromethane (2.80 mL) under

an argon atmosphere was added iodine (2.0 mg, 0.0070 mmol). After stirring at room temperature for 15 min, pyrrolidine (0.026 mL, 0.32 mmol) was added. The resulting reaction mixture was stirred at room temperature for 30 min and then filtered. The filtrate was poured into saturated aqueous $NaHSO_3$ solution, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane, 3:1) to afford β-urea **11** (31 mg, 79%) as a white gum. $[\alpha]_D^{21} = -7.4$ (c = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3389, 2955, 2876, 1746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90 (br. s, 4 H, -NCH_2-CH_2-), 2.04 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.06 (s, 3 H, OAc), 3.32 (br. s, 4 H, -NCH_2-), 3.46 (dd, J = 11.7, 10.7 Hz, 1 H, 5′-H), 4.06 (dd, J = 11.7, 5.6 Hz, 1 H, 5-H), 4.88 (t, J = 9.5 Hz, 1 H, 2-H), 4.99 (ddd, J = 10.7, 9.5, 5.6 Hz, 1 H, 4-H), 5.10 (dd, J = 9.5, 9.3 Hz, 1 H, 1-H), 5.32 (d, J = 9.3 Hz, 1 H, NH), 5.33 (t, J = 9.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.63, 20.66, 20.83, 25.35, 45.40, 64.07, 69.31, 70.87, 72.32, 80.78, 154.78, 169.79, 169.90, 171.50 ppm. $C_{16}H_{24}N_2O_8$ (372.15): calcd. C 51.61, H 6.50, N 7.52; found C 51.37, H 6.49, N 7.26.

CCDC-756982 (for **7**) and -7569783 (for **8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Spectral data for all relevant compounds, 2D ^1H–^1H COSY, spin decoupling experiments, and spin simulation.

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