Is There a Generalized Reverse Anomeric Effect? Substituent and Solvent Effects on the Configurational Equilibria of Neutral and Protonated *N*-Arylglucopyranosylamines and *N*-Aryl-5-thioglucopyranosylamines†

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The effects of substitution and solvent on the configurational equilibria of neutral and protonated *N*-(4-Y-substituted-phenyl) peracetylated 5-thioglucopyranosylamines (Y = OMe, H, CF_3, NO_2) **1**−**4** and *N*-(4-Y-substituted-phenyl) peracetylated glucopyranosylamines (Y = OMe, H, NO_2) **9**−**11** are described. The configurational equilibria were determined by direct integration of the resonances of the individual isomers in the ^{1}H NMR spectra after equilibration of both α- and *β*-isomers. The equilibrations of the neutral compounds **1**−**4** in CD_3OD, CD_3NO_2, and $(CD_3)_2CO$ were achieved by $HgCl_2$ catalysis and those of the neutral compounds **9**−**11** in CD_2Cl_2 and CD_3OD by triflic acid catalysis. The equilibrations of the protonated compounds in both the sulfur series (solvents, CD_3OD, CD_3NO_2, $(CD_3)_2CO$, $CDCl_3$, and CD_2Cl_2) and oxygen series (solvents, CD_2Cl_2 and CD_3OD) were achieved with triflic acid. The substituent and solvent effects on the equilibria are discussed in terms of steric and electrostatic effects and orbital interactions associated with the endo-anomeric effect. A generalized reverse anomeric effect does not exist in neutral or protonated *N*-aryl-5-thioglucopyranosylamines and *N*-arylglucopyranosylamines. The anomeric effect ranges from 0.85 kcal mol^{-1} in **2** to 1.54 kcal mol^{-1} in **10**. The compounds **1**−**4** and **9**−**11** show an enhanced endo-anomeric effect upon protonation, ranging from 1.73 kcal mol^{-1} in **2** to 2.57 kcal mol^{-1} in **10**. We estimate the increase in the anomeric effect upon protonation of **10** to be approximately 1.0 kcal mol^{-1}. However, this effect is offset by steric effects due to the associated counterion which we estimate to be approximately 1.2 kcal mol^{-1}. The values of K_{eq}(axial−equatorial) in protonated **1**−**4** increase in the order OMe < H < CF_3 < NO_2, in agreement with the dominance of steric effects (due to the counterion) over the endo-anomeric effect. The values of K_{eq}(axial−equatorial) in protonated **9**−**11** show the trend OMe > H < NO_2 that is explained by the balance of the endo-anomeric effect and steric effects in the individual compounds. The trends in the values of the C_1-H_1 coupling constants for **1**−**4** and the corresponding deacetylated compounds **5**−**8** as a function of substituent and α- or *β*-configuration are discussed in terms of the Perlin effect and the interplay of the endo- and exo-anomeric effects.

Introduction

The preference for the axial orientation of electronegative substituents at the anomeric carbon of a pyranose ring is in marked contrast to expectations based solely on the consideration of steric interactions. This anomalous behavior was first noted by Edward[1] in his investigation of the relative stability of methyl α- and *β*-glycopyranosides to acid hydrolysis and was clearly defined as the anomeric effect by Lemieux and Chü[2] as a result of their investigations of the anomeric equilibria of peracetylated pento- and hexopyranoses. Since that time, the anomeric effect seems to have taken on a life of its own and has engaged the imagination and efforts of both experimental and theoretical chemists in their attempts to define its nature and assign its origin.[3] The effect is stereoelectronic in nature and has since been shown to be a general effect operating in X−A−Y segments. The effect has been classified further in terms of the endo- and exo-anomeric effect. The endo-anomeric effect[4] refers to the preference of electronegative groups attached to the anomeric carbon for the axial orientation. The preference is dictated partly by stabilizing $n_X \rightarrow \sigma^*_{C-Y}$ orbital interactions (Chart 1, a).[5] The exo-anomeric effect[6] is the preference for the gauche conformation around the C_1-aglyconic carbon bond of glycopyranosides that permits expression of an $n_Y \rightarrow \sigma^*_{C-X}$ stabilizing orbital interaction (Chart 1, b and c).[5]

In recent years, another phenomenological conformational effect, the reverse anomeric effect (RAE), has also gained notoriety and has provoked some debate wherein even its very existence has been questioned. The latter effect was defined by Lemieux and Morgan[7] as the tendency of an aglycon bearing a positive charge in a

† This work is dedicated, with respect, to the memory of J. T. Edward.

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(1) Edward, J. T. *Chem. Ind. (London)* **1955**, 1102.

(2) Lemieux, R. U.; Chü, N. J. *133rd Abstr. Papers Am. Chem. Soc. Meeting* **1958**, 31N.

(3) For leading references: (a) Thatcher, G. R. J., Ed. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. (b) Juaristi, E.; Cuevas, G., Eds. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1995.

(4) Praly, J.-P.; Lemieux, R. U. *Can. J. Chem.* **1987**, *65*, 213.

(5) Pinto, B. M.; Leung, R. Y. N. *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993.

(6) Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933.

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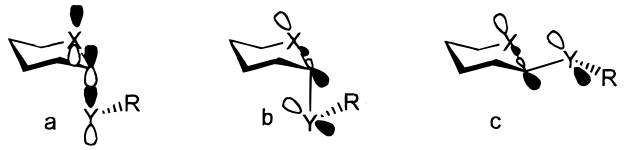
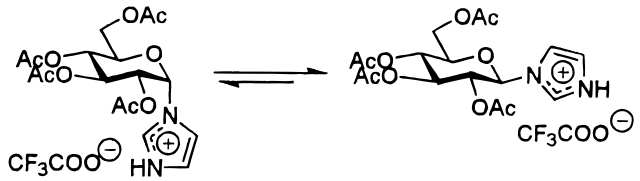
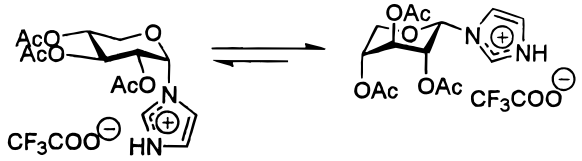
Chart 1



Scheme 1

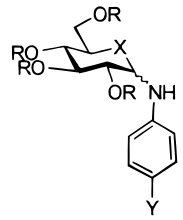


Scheme 2



sugar ring to adopt the equatorial orientation; the systems under study contained quaternary nitrogen aromatic substituents such as pyridinium and imidazolium (e.g. Scheme 1). The work was later extended by Paulsen et al.[8] to the study of the conformational equilibria in peracetylated pentopyranosyl imidazoles and the corresponding protonated species (e.g. Scheme 2) and by Finch and Nagpurkar[9] to the neutral and positively charged *N*-(hexopyranosyl)imidazoles and their tetraacetates. It has also been suggested that neutral and protonated amino and alkylamino substituents would show a RAE,[10] but this has been questioned.[5,11] The greater equatorial preferences have now been attributed to accentuated steric effects, although the conclusions are based on data from highly biased equilibria.[5,11a] A recent study with a more sterically balanced, 2,2′-substituted-1,3-dioxane system confirmed these conclusions.[11f] The general picture that is emerging from recent studies is that protonation of either an alkylamino substituent or an imidazole substituent results in a stronger anomeric effect[11a−g] and that the equatorial preference has its origin in favorable electrostatic interactions.[12] Nevertheless, the conclusions were not universal and appeared to be system-dependent. Thus, whereas Perrin and coworkers[11a,b] claimed an absence of a RAE with protonated *N*-(glucopyranosyl)imidazoles (Scheme 1) by examination of configurational equilibria using an NMR titration

Chart 2



Compound	R	X	Y
1	Ac	S	OMe
2	Ac	S	H
3	Ac	S	CF_3
4	Ac	S	NO_2
5	H	S	OMe
6	H	S	H
7	H	S	CF_3
8	H	S	NO_2
9	Ac	O	OMe
10	Ac	O	H
11	Ac	O	NO_2

method, the Queen's group[12] claimed the existence of such an effect in protonated *N*-(xylopyranosyl)imidazoles (Scheme 2) by examination of conformational equilibria using an approximate average coupling-constant method, which they attributed to intramolecular electrostatic attraction in the equatorial isomers. Such subtle differences indicate that the magnitude of the measured effect is small. The matter has been resolved very recently by use of an NMR titration method to estimate the RAE in protonated *N*-(xylopyranosyl)imidazoles.[11g] The authors conclude that no RAE exists in these compounds and that the previous conclusions[8,9,12b] resulted because of the approximations inherent in the average coupling-constant method.[11g]

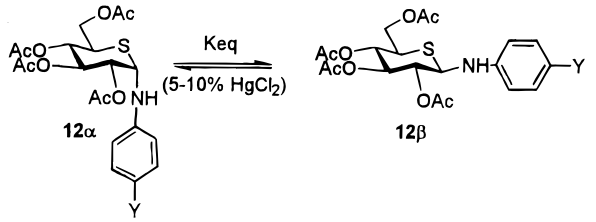
We chose to address the question of the existence of a *generalized* RAE by systematic examination of substituent and solvent effects on the configurational equilibria of *N*-aryl-5-thioglucopyranosylamines **1**−**4** and *N*-arylglucopyranosylamines **9**−**11** and the corresponding protonated species (Chart 2). The 5-thio compounds **1**−**4** are more stable than their oxygen congeners **9**−**11** and are readily amenable to analysis. Both series also display equilibria that are not highly biased and differ from systems studied to date; they constitute, therefore, a valuable test system. The question of a generalized RAE is of interest for an understanding of the enzyme inhibitory activity of glucopyranosylamines and their 5-thio analogues.[13]

Results and Discussion

Configurational Analysis. The equilibrium populations of the 5-thio compounds **1**−**4** and their protonated derivatives were assessed by ^{1}H NMR spectroscopy at 294 K. Equilibration of the neutral species (**12**, Scheme 3) was achieved by the $HgCl_2$ catalysis of the individual isomers in the polar solvents CD_3OD, CD_3NO_2, and $(CD_3)_2CO$ only, owing to the limited solubility of $HgCl_2$ in nonpolar solvents. The equilibria were approached from both directions, i.e., starting from pure α- or β-anomers, to ensure that a true equilibrium had been

(7) (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205. (b) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527.
(8) (a) Paulsen H.; Gyorgydeak, Z.; Friedmann, M. *Chem. Ber.* **1974**, *107*, 1590. (b) Paulsen, H. *Die Starke* **1975**, *27*, 397.
(9) Finch, P.; Nagpurkar, A. G. *Carbohydr. Res.* **1976**, *49*, 275.
(10) (a) Wolfe, S.; Whangbo, M.-H.; Mitchell, D. J. *Carbohydr. Res.* **1979**, *69*, 1. (b) Krol, M. C.; Huige, C. H. J.; Altona, C. *J. Comput. Chem.* **1990**, *11*, 765.
(11) (a) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 6825. (b) Fabian, M. A.; Perrin, C. L.; Sinnott, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 8398. (c) Perrin. C. L.; Fabian, M. A.; Armstrong, K. B. *J. Org. Chem.* **1994**, *59*, 5246. (d) Perrin, C. L. *Pure Appl. Chem.* **1995**, *67*, 719. (e) Perrin, C. L. *Tetrahedron* **1995**, *51*, 11901. (f) Jones, P. G.; Kirby, A. J.; Komarov, I. V.; Wothers, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 1695. (g) Perrin, C. L.; Fabian, M. A.; Brunckova, J.; Ohta, B. K. *J. Am. Chem. Soc.* **1999**, *121*, 6911.
(12) (a) Chan, S. S. C.; Szarek, W. A.; Thatcher, G. R. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 45. (b) Vaino, A. R.; Chan, S. S. C.; Szarek, W. A.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 4514.
(13) (a) Andrews, J. S.; Weimar, T.; Frandsen, T. P.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 10799. (b) Randell, K. D.; Frandsen, T. P.; Stoffer, B.; Johnson, M. A.; Svensson, B.; Pinto, B. M. *Carbohydr. Res.* **1999**, *321*, 143.

Scheme 3



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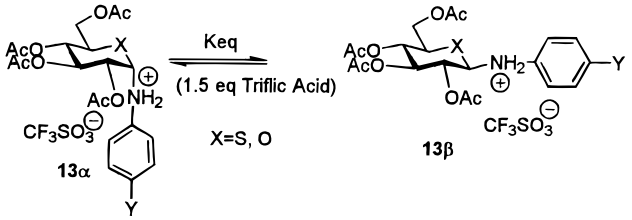
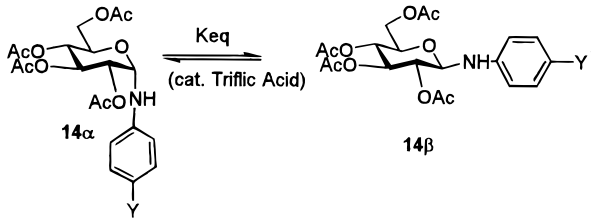


Scheme 5



reached. The corresponding equilibrations of the protonated species (**13**, Scheme 4) were studied in the presence of 1.5 equiv of triflic acid, in polar and nonpolar solvents. The addition of 1.5 equiv of triflic acid would ensure complete protonation of the amines since the pK_a of triflic acid is -5.9[14] while the pK_as of the isolated aglycons are 5.31 for *p*-anisidine, 4.60 for aniline, 2.45 for *p*-trifluoromethylaniline, and 1.00 for the weakest base, *p*-nitroaniline.[15] The equilibration of the oxygen congeners **9**−**11** was performed at 230 K only in CD_2Cl_2 and CD_3OD. In this series of compounds, we were restricted in our choice of solvents because of the instability of the compounds or line broadening effects in the spectra which did not permit unambiguous assignment of signals or their accurate integration. The equilibrations of the neutral species (**14**, Scheme 5) were achieved by addition of catalytic amounts of triflic acid to solutions of the individual anomers, and those of the protonated species (**13**, Scheme 4) were achieved by addition of excess triflic acid, as described above. The equilibrium constants and free energy values for **1**−**4** are listed in Table 1 and those for **9**−**11** in Table 2.

Equilibration of the 5-Thio Compounds 1−4. Examination of the equilibria of the neutral species **1**−**4** in polar solvents indicates that there is no marked substituent or solvent effect. Interestingly, the effects of protonation on the equilibria are a function of the substituent. When Y = OMe (**1**) or H (**2**), the proportion of the axial isomer (**13**α, Scheme 4) increases upon protonation. This can be attributed to an increase in the endo-anomeric effect because the strength of the n-σ^* interactions increases due to a smaller energy gap between interacting fragment orbitals (see Scheme 6).[10] When Y = CF_3 (**3**) or NO_2 (**4**), there is no significant change in K_{eq} upon protonation. The positive charge on nitrogen must enhance the endo-anomeric effect as above. However, since the nitrogen atom bears a greater positive charge because of the inductive and field effects of these substituents, we suggest that the counterion is bound more tightly and that there is an *increased* steric effect that offsets the increased anomeric effect (see Scheme 7). Corroboration of this hypothesis derives from the effects of substituents and solvent on the equilibria of the protonated species. Thus, when Y = OMe (**1**) or H (**2**), the axial isomer (**13**α, Scheme 4) dominates for all solvents and the endo-anomeric effect is pronounced. One predicts that the *p*-OMe substituent will cause the nitrogen to be less positive, and therefore, the endo-anomeric effect will not be as strong as in the parent aniline derivative **2**.[16] One also predicts that the counterion will not be as tightly bound and that steric effects will be less pronounced. The observation of a greater proportion of the axial isomer for **1** (Y = OMe) than **2** (Y = H) suggests that the steric effects dominate. When Y = CF_3 (**3**) or NO_2 (**4**), the *β*-isomer (**13***β*, Scheme 4) is favored more than in the compounds in which Y = OMe (**1**) or H (**2**). The observation supports our argument that the electron-withdrawing substituents cause the nitrogen atom to have a greater positive charge, a tightly bound counterion, and, therefore, a greater steric effect (see Scheme 7); these increased steric effects favor the equatorial isomer (**13***β*, Scheme 4). In nonpolar solvents, the steric effect of the associated counterion should be even more significant because the ion-pair is not solvated effectively. In accord with this hypothesis, when Y = CF_3 (**3**) or NO_2 (**4**), there is a greater proportion of the *β*-isomer in nonpolar solvents than in polar solvents; this effect is more pronounced than for compounds in which Y = OMe (**1**) or H (**2**). In **3** and **4**, the counterion is bound more tightly and these equilibria are more sensitive to the effects of solvent. The values of K_{eq} increase in the order OMe < H < CF_3 < NO_2, in agreement with the dominance of steric effects (due to the counterion) over the endo-anomeric effect.

Equilibration of the Oxygen Congeners 9−11. The percentages of the *β*-isomers in compounds **9**−**11** are greater than in the corresponding sulfur analogues, in accord with the greater steric effects in the former series. As was the case with the 5-thio compounds **1**−**4**, there is no marked substituent effect on the equilibria of the neutral species. However, in this series we were able to examine the equilibria in both a nonpolar and polar solvent and there is a notable solvent effect: the proportion of the α-anomer is greater in CD_2Cl_2 compared to CD_3OD. We attribute this effect to the lesser ability of the nonpolar solvent CD_2Cl_2 to solvate the dipole−dipole interactions in the *β*-anomers that are normally associated with the endo-anomeric effect (see Scheme 8). There was also a greater proportion of the *β*-isomer for **9**−**11** in CD_3NO_2 than in CD_2Cl_2 (data not shown). The greater effect of dipolar interactions in the oxygen series as compared to the sulfur series is expected on the basis of the greater electronegativity of oxygen than sulfur.

The effects of protonation and the effects of solvent on the equilibria of the protonated species reveal some interesting trends. Unfortunately, the comparison is only

(14) Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 2342.
(15) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworth: London, 1965.
(16) Pinto, B. M.; Johnston, B. D.; Sandoval-Ramirez, J.; Sharma, R. D. *J. Org. Chem.* **1988**, *53*, 3766.

Table 1. Effects of Protonation, Solvent, and Substituent on K_{eq} and ΔG for the Neutral Compounds in Which X = S

			neutral		protonated	
solvent	compd	Y	K_{eq} (error)	ΔG^a (error)	K_{eq} (error)	ΔG^a (error)
CD_3NO_2	**1**	OMe	1.31 (0.15)	−0.16 (0.07)	0.32 (0.07)	0.67 (0.10)
	2	H	1.26 (0.08)	−0.14 (0.04)	0.45 (0.15)	0.47 (0.20)
	3	CF_3	1.15 (0.13)	−0.08 (0.07)	1.05 (0.08)	−0.03 (0.04)
	4	NO_2	1.51 (0.10)	−0.24 (0.04)	1.27 (0.07)	−0.14 (0.03)
CD_3OD	**1**	OMe	1.37 (0.10)	−0.18 (0.04)	*b*	*b*
	2	H	1.22 (0.08)	−0.12 (0.03)	*b*	*b*
	3	CF_3	1.24 (0.19)	−0.13 (0.09)	0.97 (0.09)[c]	0.02 (0.05)[c]
	4	NO_2	1.34 (0.16)	−0.17 (0.01)	*b*	*b*
$(CD_3)_2CO$	**1**	OMe	1.15 (0.08)	−0.08 (0.04)	0.38 (0.11)	0.56 (0.17)
	2	H	1.15 (0.06)	−0.08 (0.03)	0.81 (0.13)	0.12 (0.09)
	3	CF_3	0.98 (0.07)	0.01 (0.04)	1.07 (0.08)	−0.04 (0.04)
	4	NO_2	0.98 (0.08)	0.01 (0.05)	*b*	*b*
$CDCl_3$	**1**	OMe	*d*	*d*	0.48 (0.13)	0.43 (0.10)
	2	H	*d*	*d*	0.81 (0.08)	0.13 (0.06)
	3	CF_3	*d*	*d*	1.69 (0.09)	−0.31 (0.02)
	4	NO_2	*d*	*d*	1.93 (0.14)	−0.39 (0.04)
CD_2Cl_2	**1**	OMe	*d*	*d*	0.32 (0.03)	0.68 (0.05)
	2	H	*d*	*d*	0.65 (0.03)	0.26 (0.03)
	3	CF_3	*d*	*d*	1.40 (0.12)	−0.20 (0.05)
	4	NO_2	*d*	*d*	1.71 (0.07)	−0.31 (0.02)

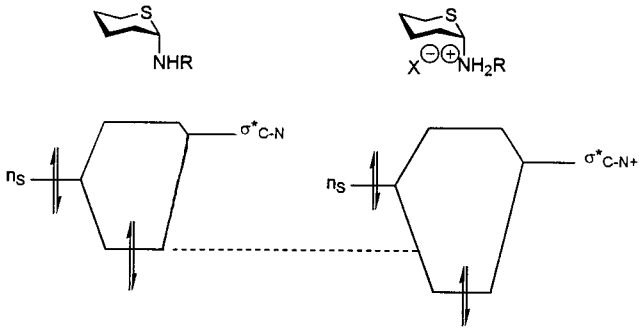
[a] In kcal mol^{-1} at 294 K. [b] Decomposition of samples did not permit accurate determination of K_{eq}. [c] Only equilibrated from α→β (3 days). [d] Equilibration of the neutral species in these solvents was not possible owing to the insolubility of $HgCl_2$.

Table 2. Effects of Protonation, Solvent, and Substituent on K_{eq} and ΔG for the Neutral Compounds in Which X = O

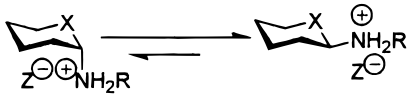
			neutral		protonated	
solvent	compd	Y	K_{eq} (error)	ΔG^a (error)	K_{eq} (error)	ΔG^a (error)
CD_2Cl_2	**9**	OMe	2.65 (0.03)	−0.45 (0.01)	6.00 (0.09)	−0.82 (0.01)
	10	H	2.74 (0.07)	−0.46 (0.01)	4.24 (0.07)	−0.66 (0.01)
	11	NO_2	3.18 (0.03)	−0.53 (0.01)	6.58 (0.03)	−0.82 (0.01)
CD_3OD	**9**	OMe	4.04 (0.11)	−0.64 (0.02)	6.87 (0.25)	−0.88 (0.03)
	10	H	3.95 (0.06)	−0.63 (0.01)	3.87 (0.06)	−0.62 (0.01)
	11	NO_2	*b*	*b*	10.9 (0.20)	−1.09 (0.03)

[a] In kcal mol^{-1} at 230 K. [b] No observable α-isomer.

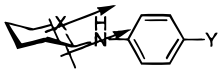
Scheme 6



Scheme 7



Scheme 8



possible for the equilibrations in CD_3OD and CD_2Cl_2 since attempts to extend these studies to other solvents, e.g. CD_3NO_2, were frustrated by problems of line broadening that made assignment of the signals ambiguous and integrations inprecise. When Y = H (**10**), there is no effect upon protonation in CD_3OD, but in CD_2Cl_2 more of the β-isomer is observed. We attribute this to the solvation or damping by the polar solvent of the favorable dipole−monopole interaction between the resultant dipole of the lone pairs on the ring oxygen and the positive monopole on the protonated nitrogen atom in the β-isomer. When Y = OMe (**9**), there is an increase in the proportion of the β-isomer upon protonation in both solvents. When Y = NO_2 (**11**), the α-isomer is barely detectable in the neutral compound, but in CD_3OD, the α-isomer is present in the protonated form. The positive charge must enhance the endo-anomeric effect, as no α-isomer is present in the unprotonated species. The more pronounced α-preference in CD_3OD relative to CD_2Cl_2 likely results from better solvation of the dipole−monopole interactions in the β-isomer. Since the nitrogen atom is more positive in this compound because of the substituent, we propose that the counterion is more tightly bound and that there is an increased steric effect that offsets the increased endo-anomeric effect (see Scheme 7).

It is instructive to compare the effects of substituents on the equilibria of the protonated species, as with the sulfur series of compounds. When Y = H (**10**), there is a greater proportion of the α-isomer present as compared to the compounds in which Y = OMe (**9**) or NO_2 (**11**). With regard to the *p*-OMe compound **9**, one predicts again that the substituent will cause the nitrogen to be less positive, and therefore, the anomeric effect will not be as strong as in the parent aniline derivative **10**.[16] One also predicts that the counterion will not be as tightly bound and that steric effects will be less pronounced. The observation of a greater proportion of the α-isomer for **10** (Y = H) than **9** (Y = OMe) suggests that the endo-anomeric effect dominates, in contrast to the situation with the sulfur

Scheme 9

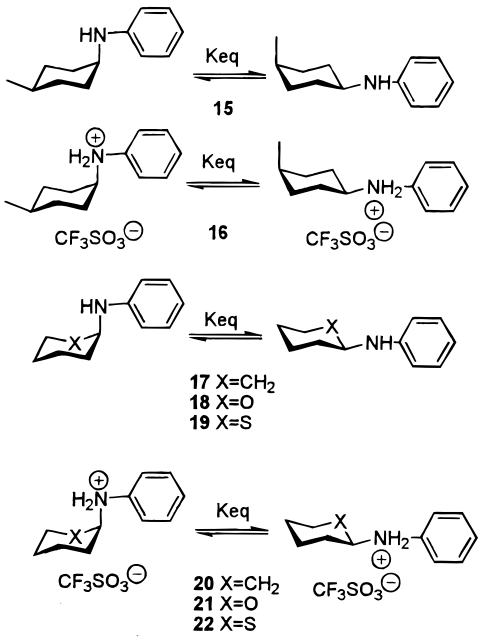


Table 3. Equilibrium Data for 15 and 16[a]

	K_{eq} (error)	ΔG (error)[b]
15	0.18 (0.01)[c]	0.54 (0.01)
16	2.03 (0.01)[d]	−0.23 (0.01)

[a] In CD_2Cl_2:$CFCl_3$ (85:15). [b] In kcal mol^{-1} at 160 K. [c] Derived from integration of signals for $H1_{axial}$ (δ 3.20), NH (δ 3.60) in the minor conformer and $H1_{equatorial}$ (δ 3.70), NH (δ 3.94) in the major conformer. [d] Derived from integration of signals for $H1_{axial}$ (δ 3.17) in the major conformer and $H1_{equatorial}$ (δ 3.68) in the minor conformer.

series. With regard to the *p*-NO_2 compound **11**, the β-isomer (**13**β, Scheme 4) is favored more than in the compounds in which Y = OMe (**9**) or H (**10**). As with the sulfur series, the observation supports our argument that the electron-withdrawing substituents cause the nitrogen atom to have a greater positive charge, a tightly bound counterion, and therefore, a greater steric effect (see Scheme 7); these increased steric effects favor the equatorial isomer (**13**β, Scheme 4).

The results presented in the foregoing sections suggest that there is no generalized reverse anomeric effect operating in X−C−N or X−C−N^+ fragments. In fact, protonation leads to a greater endo-anomeric effect than in the corresponding neutral X−C−N fragments. The effects of substitution on the equilibria of the protonated species can be interpreted in terms of the dominance of steric effects (due to the counterion) over the endo-anomeric effect. For compounds **1**−**4**, in nonpolar solvents, ion pair separation is not as effective and the accentuated steric effects are more pronounced when X = CF_3 or NO_2 than when X = H or OMe.

The Anomeric Effect. To estimate the magnitudes of the anomeric effects in **1**−**4** and **9**−**11**, *cis*-4-methyl-1-*N*-phenylcyclohexylamine **15** was used as a model compound in order to approximate the steric component. The methyl group was used as a counterpoise group to give a more balanced conformational equilibrium, and the conformational equilibria of **15** and the corresponding protonated species **16** (Scheme 9) were analyzed at 160 K in a mixture of CD_2Cl_2:$CFCl_3$ (85:15) (see Table 3). The *A*-value of the methyl group (1.80 ± 0.02 kcal mol^{-1}, 157 K)[17] was then used to give an estimate of the conformational free energy for *N*-phenylcyclohexylamine **17** and its protonated counterpart **20**. These data (Table 4) give an estimate of approximately 0.8 kcal mol^{-1} for the steric effect upon protonation that can be used as a rough measure of the steric effect of the associated counterion. The steric components of the conformational free energies for *N*-phenyltetrahydropyranylamine **18** and its protonated counterpart **21**, and *N*-phenyltetrahydrothiapyranylamine **19** and its protonated counterpart **22** were then calculated (see Table 4) by taking into account the ratios of the respective conformational free energies for the axial−equatorial equilibria in 2-Me-tetrahydropyran (2.86 ± 0.20 kcal mol^{-1}),[18] 2-Me-tetrahydrothiapyran (1.42 ± 0.07 kcal mol^{-1}),[19] and methylcyclohexane (1.80 ± 0.02 kcal mol^{-1}).[17] Finally, estimates of the anomeric effects operating in the neutral and protonated compounds **2** and **10** were obtained by adding the steric components to the conformational free energies (Tables 1 and 2) for neutral and protonated **2** and **10** (see Table 5). We realize that different temperatures were used to obtain the different ΔG values described above, but feel that the treatment will provide a rough estimate of the magnitude of the anomeric effect. For the neutral compounds, the anomeric effect ranges from 0.85 kcal mol^{-1} in **2** to 1.54 kcal mol^{-1} in **10**. We have shown that in the equilibria of the protonated species, the associated counterion is critical in determining the steric effect and that the solvent and substituent play a crucial role in the solvation of ion pairs and hence the steric effect. Therefore, since we have only assessed the steric component for the protonated, unsubstituted compound **16** in a nonpolar solvent, we have only estimated the magnitudes of the anomeric effect for the protonated, unsubstituted compounds **2** and **10** in the nonpolar solvents $CDCl_3$ and CD_2Cl_2. The anomeric effect in the protonated derivatives ranges from 1.73 kcal mol^{-1} in **2** to 2.57 kcal mol^{-1} in **10**. In the case of **10**, the anomeric effect increases on protonation by approximately 1.0 kcal mol^{-1}. This is offset by a steric effect of the associated counterion of

Table 4. Steric Component of ΔG in 17−22[a]

compd	$-\Delta G$
17	1.26 (0.10)
18	2.00 (0.14)
19	0.99 (0.05)
20	2.03 (0.02)
21	3.23 (0.23)
22	1.60 (0.08)

[a] In kcal mol^{-1}.

Table 5. Anomeric Effect in Compounds 2 and 10[a]

compd	solvent	neutral	protonated
2	CD_3NO_2	0.85 (0.06)	*b*
2	CD_3OD	0.87 (0.06)	*b*
2	$(CD_3)_2CO$	0.91 (0.06)	*b*
2	$CDCl_3$	*c*	1.73 (0.08)
2	CD_2Cl_2	*c*	1.86 (0.08)
10	CD_3OD	1.37 (0.14)	*b*
10	CD_2Cl_2	1.54 (0.14)	2.57 (0.23)

[a] In kcal mol^{-1}. [b] Not appropriate (see text). [c] Experiments not performed because of limited solubility of $HgCl_2$.

(17) Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLeon, E. L.; Jarret, R. M. *J. Org. Chem.* **1999**, *64*, 2085.
(18) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635.
(19) Willer, R. L.; Eliel, E. L. *J. Am. Chem. Soc.* **1977**, *99*, 1925.

Table 6. Coupling Constants J_{C1-H1} (Hz) for Compounds 1−8

compd (Y; R)	J_{C1-H1} α	J_{C1-H1} β
1 (OMe; Ac)	153.9	156.2
2 (H; Ac)	154.5	151.7
3 (CF_3; Ac)	154.4	155.9
4 (NO_2; Ac)	154.9	154.5
5 (OMe; H)	152.8	156.4
6 (H; H)	152.9	149.5
7 (CF_3; H)	151.0	151.2
8 (NO_2; H)	152.0	152.1

about 1.2 kcal mol^{-1}. Unfortunately, in the case of **2**, the equilibrium data for the neutral species in CD_2Cl_2 are not available, and an estimate of the magnitude of the differential anomeric effect on protonation is not possible. Nevertheless, the results indicate that the reverse anomeric effect does not exist in both neutral and protonated *N*-phenylglucopyranosylamine **10** and in protonated *N*-phenyl-5-thioglucopyranosylamine **2**; rather, the anomeric effect exists.

Perlin Effect. As a final point of interest, we comment here on the J_{C1-H1} coupling constants in compounds **1**−**8** and their relationship to the Perlin effect, which correlates larger J_{C1-H1} values with greater C−H bond strengths.[20] The data are summarized in Table 6. The trends are the same for the acetylated and free sugars. The *p*-CF_3 and *p*-NO_2 derivatives (**3**, **4**, **7**, **8**) have similar coupling constants for both the α- and the β-isomers. The *p*-OMe derivatives (**1**, **5**) have larger coupling constants for the β-isomer, whereas the aniline derivatives (**2**, **6**) have larger coupling constants for the α-isomer. Compounds **2** and **6** follow the normal trend in that an $n_S \rightarrow \sigma^*_{C-H1}$ orbital interaction in the β-isomers results in weaker C−H bonds and smaller coupling constants.[20]

We propose that in the case of the *p*-OMe derivatives β-**1** and β-**5**, a greater exo-anomeric effect ($n_N \rightarrow \sigma^*_{C-S}$) relative to that in the unsubstituted compounds **2** and **6**, respectively,[16] leads to greater s-character in the C−H bond and to a reversal in C_1-H_1 bond strengths. This effect outweighs the opposing bond lengthening effect caused by the Perlin effect.

Within the series of the acetylated α-isomers the J_{C1-H1} values are very similar, in contrast to those for the β-isomers which increase in **1**, **3**, and **4** relative to the value for the unsubstituted compound **2**, the greatest difference being observed for the *p*-OMe derivative **1**. Similar trends are observed for the α- and β-isomers in the deprotected compounds **5**−**8**. The larger coupling constants in the *p*-OMe derivatives β-**1** or β-**5** can be readily rationalized in terms of a greater exo-anomeric effect, which leads to greater C−H bond strengths (see above). The origins of the increases in J_{C1-H1} values for the *p*-CF_3 and *p*-NO_2 β-compounds are not as readily obvious. In these cases, the exo-anomeric effect is reduced.[16] We propose that these substituents cause field effects and inductive effects that cause a contraction of the C−H bond. The effect can be viewed as an electrostatic effect, as proposed by Pross and Radom[21] for the case of acetals. The invariance of the J_{C1-H1} values in the α-isomers may be attributed to the counterbalance of the endo- and exo-anomeric effects. For example, the greater endo-anomeric effect in **8** relative to that in **6** is offset by the decreased exo-anomeric effect.[14] The two effects thus partially cancel in **8**, giving a C−H bond strength that is similar to that in **6**.

Conclusions

There is no evidence to support the existence of a generalized reverse anomeric effect in neutral or protonated *N*-aryl-5-thioglucopyranosylamines and *N*-arylglucopyranosylamines. For the neutral compounds, the anomeric effect ranges from 0.85 kcal mol^{-1} in **2** to 1.54 kcal mol^{-1} in **10**. The compounds **1**−**4** and **9**−**11** show an enhanced endo-anomeric effect upon protonation. The anomeric effect in the protonated derivatives ranges from 1.73 kcal mol^{-1} in **2** to 2.57 kcal mol^{-1} in **10**. We estimate the increase in the anomeric effect upon protonation of **10** to be approximately 1.0 kcal mol^{-1}. However, this effect is offset by steric effects due to the associated counterion which we estimate to be approximately 1.2 kcal mol^{-1}. The values of K_{eq} in protonated **1**−**4** increase in the order OMe < H < CF_3 < NO_2, in agreement with the dominance of steric effects (due to the counterion) over the endo-anomeric effect. The values of K_{eq} in protonated **9**−**11** show the trend OMe > H < NO_2 that is explained by the balance of the endo-anomeric effect and steric effects in the individual compounds.

Experimental Section

The synthesis of compounds **1**−**8** are described elsewhere.[13b] Compounds **9**−**11** were synthesized by the method of Honeyman.[22] The α- and β-isomers of **10** and **11** have been characterized previously.[23] The synthesis of α- and β-**9** is described below. Compound **15** was synthesized as described.[24]

^{1}H NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer at 400.13 MHz. Chemical shifts are given in ppm downfield from TMS. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. Chemical shifts of the neutral and protonated species **1**−**4** and **9**−**11** are listed in Tables 7−10 of the Supporting Information.

***N*-(4-Methoxyphenyl)-2,3,4,6-tetra-*O*-acetyl-α- and β-D-glucopyranosylamine 9α and 9β.** A mixture of D-glucose (9.01 g, 50.0 mmol), *p*-anisidine (6.16 g, 50.0 mmol) in methanol (100 mL), and glacial acetic acid (0.2 g) was refluxed for 45 min. The reaction mixture was concentrated to give a red oil which was shown by ^{1}H NMR spectroscopy to contain a mixture of α- and β-isomers. The oil was dissolved in pyridine (80 mL) and acetic anhydride (60 mL) containing a catalytic amount of DMAP and the mixture was stirred for 1 h at room temperature and then for 45 min at 45 °C. The reaction mixture was poured into ice/water (800 mL) and stirred to give a reddish-brown precipitate that was recrystallized from ether to give a 2:1 α:β mixture of **9** (13.5 g, 64%). Selective recrystallization from ethanol gave pure **9**α (mp 131−132 °C) and pure **9**β (mp 140−141 °C). Anal. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.63; H, 6.00; N, 3.09. Found (α:β mixture): C, 55.66; H, 6.02; N, 3.08.

The equilibrations of the neutral compounds **1**−**4** were carried out at 294 K in CD_3NO_2, CD_3OD, and $(CD_3)_2CO$. To a solution of either the α- or β-isomer (1.5 mg) in 0.6 mL of the appropriate deuterated solvent was added 10% $HgCl_2$ from a 100 mM stock solution in deuterated solvent. The equilibra-

(20) (a) Wolfe, S.; Pinto, B. M.; Varma, V.; Leung, R. Y. N. *Can. J. Chem.* **1990**, *68*, 1051. (b) Juaristi, E.; Cuevas, G. *Tetrahedron Lett.* **1992**, *33*, 1847. (c) Juaristi, E.; Cuevas, G.; Flores-Vela, A. *Tetrahedron Lett.* **1992**, *33*, 6927. (d) Cuevas, G.; Juaristi, E.; Vela, A. *J. Phys. Chem.* **1999**, *103*, 932.

(21) Pross, A.; Radom, L. *J. Comput. Chem.* **1980**, *1*, 295.

(22) Honeyman, J. *Methods Carbohydr. Chem.* **1963**, *2*, 95.

(23) (a) Capon, B.; Connett, B. E. *J. Chem. Soc.* **1965**, 4492. (b) Capon, B.; Connett, B. E. *J. Chem. Soc.* **1965**, 4497.

(24) Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412.

tions of the protonated compounds **1**−**4** were carried out at 294 K in $CDCl_3$, CD_2Cl_2, CD_3NO_2, CD_3OD, and $(CD_3)_2CO$. To a solution of either the α- or *β*-isomer (1.5 mg) in 0.6 mL of the appropriate deuterated solvent was added 1.5 equiv of triflic acid from a 0.565 M stock solution in deuterated solvent. The ^{1}H NMR spectra were recorded periodically until equilibrium had been reached. Equilibration usually took place in less than a few hours. Because both isomers were used in the equilibrations, it was deemed that equilbrium had been reached when the spectra starting from both the α- and the *β*-isomers were identical.

The equilibrations of the neutral and protonated compounds **9**−**11** were carried out at 230 K in CD_2Cl_2 and CD_3OD. Attempts to extend these studies to other solvents, e.g. CD_3NO_2, were frustrated by line broadening effects that did not permit unambiguous assignment of the signals or their accurate integration. To a solution of either the α- or *β*-isomer (10 mg) in 0.6 mL of the appropriate deuterated solvent at 230 K was added 5% triflic acid for the equilibrations of the neutral species or 2.5 equiv of triflic acid for the equilibriations of the protonated species. The equilibrations were immediate, and the proton spectra did not change over time.

The equilibrium constants were derived from the integration of different pairs of peaks of both isomers. Isolated signals were integrated to ensure accuracy. The average values of several integrations were taken into account for the final calculation of *K*. The errors in *K* are the standard deviations of the measurements. The errors in ΔG were derived from errors in *K* and in temperature (±2 K). Calculations of the magnitude of the anomeric effect were performed using the formula: $AE = \Delta G_2 - \alpha(\Delta G_1)$, where $\alpha = \Delta G$(2-methyltetrahydropyran or 2-methyltetrahydrothiapyran)/ΔG(methylcyclohexane); $\Delta G_1 =$ *N*-(phenyl)cyclohexylamine; $\Delta G_2 =$ *N*-arylglycopyranosylamine (X = S, O). The errors in the values of ΔG in Tables 4 and 5 were derived by standard treatment for the propagation of errors.

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Supporting Information Available: Tables of ^{1}H NMR chemical shifts for neutral and protonated **1**−**4** and **9**−**11** in different solvents. This material is available free of charge via the Internet at http://pubs.acs.org.

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