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NMR Studies and Semiempirical Calculations on the Structure of Glycoamidines

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Abstract: The configuration and conformation of glycoamidines in solution have been studied by a combination of NMR data (proton and carbon chemical shifts, coupling constants, NOEs, and variable temperature experiments), and MNDO-PM3 semiempirical calculations. Copyright © 1996 Elsevier Science Ltd

Key Words: Amidine, glycoconjugate, NMR experiments, semiempirical calculations.

INTRODUCTION

Recent reports have disclosed that carbohydrate-based amidines, namely glycoamidines, are important functional components of lipopolysaccharides (LPS)[1-3] and naturally-occurring glycosidase inhibitors.[4,5] In connection with the latter, series of amidine saccharides[6] and pseudodisaccharides[7] that share some structural features of natural inhibitors, have been synthesized. These findings have prompted us to investigate the structure and conformation of glycoamidines in solution, in order to characterize thoroughly such sugar derivatives and provide tentative rules for their stereochemical assignment.

Initially, the structural determination of natural glycoamidines was the subject of controversy. Thus, the *N*-acetylimidoyl group of LPS found in *Pseudomonas* species was thought to be an imidoyl moiety.[8] Likewise, the glycosidase inhibitor isolated from *Amycolatopsis trehalostatica* cultures, denoted as trehalostatin, resulted to be identical with trehalozin, the natural inhibitor isolated from *Micromonospora* strains.[4,5]

The amidine group offers some intriguing structural arrangements: a) *N*-monosubstituted amidines can display two tautomeric forms, whose relative stabilities have been frequently explained by stereoelectronic effects.[9] b) *Z* and *E* configurations around the C=N double bond are also possible, being the *E*-isomers thermodynamic control compounds, albeit some *Z*-isomers have been eventually isolated.[10] c) The rotational barrier around the C-N bond of amidines lies in the range 50-80 kJ/mol.[11] These values are generally greater than those of enamines and anilines and lesser than those of amides,[12] taking into account that all of them show

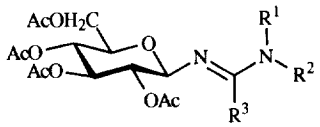
the common arrangement $R^1(X=)C\text{-}NR^2R^3$. d) Conformations around the C-NCN bonds have not been determined with the exception of a study on aryl amidines.[13]

For glycoamidines, the conformation around the anomeric bond should also play an important role in a similar way to *N*-nucleosides and *O*-glycosides for which their activity correlates with the preferred conformation in solution.[14] The anomeric[15,16] and *exo*-anomeric[17] effects have been invoked to state the preferred orientation of the aglycon.

In our continuing efforts in this area, we have proposed a set of NMR parameters that enable the assignments of *Z/E* configurations and conformations of (thio)amidosugars.[18] Likewise we reported recently a simple entry to monosaccharide amidines.[19] Now, NMR spectroscopy along with semiempirical calculations have been utilized to characterize the overall shape of glycoamidines in solution. The semiempirical MNDO-PM3 method[20,21] has been utilized for the optimization of geometries and the calculations of heats of formation.

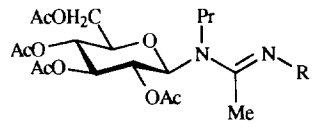
RESULTS AND DISCUSSION

In our study, three series of simple glycoamidines have been evaluated. Series I (compounds **1-3**) and series II (compounds **4-6**) have been classified according to the double bond position. Compounds of series III (**7-10**) can also exhibit a tautomeric equilibrium.



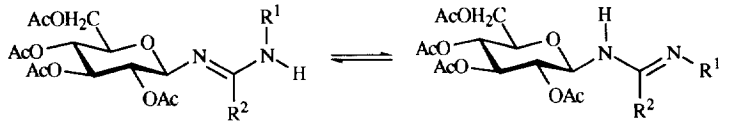
1 $R^1 = R^2 = Et$, $R^3 = Me$
2 $R^1 = Bn$, $R^2 = R^3 = Me$
3 $R^1 = R^2 = -(CH_2)_5-$, $R^3 = H$

series I



4 R = *i*-Pr
5 R = Pr
6 R = Ph

series II



7 $R^1 = Bn$, $R^2 = Me$
8 $R^1 = i\text{-}Pr$, $R^2 = H$
9 $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = Me$
10 $R^1 = Ph$, $R^2 = Me$

series III

Only series III amidines exhibit the valuable H-1,NH coupling though NOE measurements can represent an alternative tool for the conformational analysis of such substances. NOE values between H-1 or H-2 protons and those of vicinal substituents at the amidine function can be utilized to estimate the dihedral angle around the glycosidic bond. In some instances, however, NMR data alone do not provide definitive conclusions, so that a theoretical study of a series of simplified models was undertaken in order to determine their geometries and heats of formation for comparative purposes. The torsional angles Φ and φ around the glycosidic (C1-N) and

the amidine single bonds, respectively, should be considered in the aglycon moiety (Fig. 1). The latter dihedral angle, φ, determines the possible *s-E* or *S-Z* conformations of the amidine.

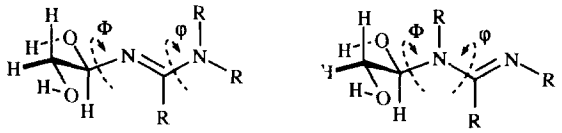


Figure 1

Calculations were carried out assuming rotations with 30° increments around the glycosidic bond with full optimization for the rest of parameters of the amidine group. The abbreviated sugar moiety was fixed in the conformation displayed in Figure 2 in order to avoid the influence of its conformational changes on the enthalpies of formation of each rotamer. The starting value of Φ = 0° refers to a conformation for which the O-C1 and N-$C_{amidine}$ bonds are eclipsed (see Figure 2).

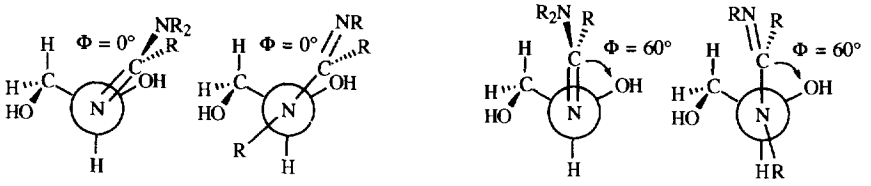
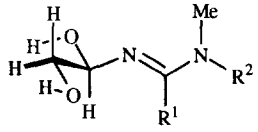


Figure 2

Series I. Models **11** and **12** do reflect the structural arrangements found in glycoamidines **1** and **3**, that is the possibility of *E* or *Z* isomerism around the double bond as well as the conformation around the glycosidic bond. Figure 3 shows that *E* isomers are always more stable than their *Z* counterparts whichever conformation is considered, and two conformational minima are located in the ranges 30° < Φ < 90° and 210° < Φ < 300°. Figure 3 also displays enthalpy maxima for models **11** and **12** for conformations in which the dihedral angle Φ is close to 150°, which may be attributed to steric hindrance with the hydroxyl substituent at the C2 position of the pseudosugar structure.



11 $R^1 = R^2 = Me$
12 $R^1 = H$, $R^2 = Me$
13 $R^1 = Me$, $R^2 = Et$

Disubstitution with different alkyl groups at the *N'* atom implies that *s-E* and *s-Z* conformers should be further taken into account. Figure 4 plots the enthalpies of formation *versus* the torsional angle Φ for the possible stereostructures of model **13** that mimics the glycoamidine **2**. Again, *E*-isomers are the most stable compounds albeit the structures *E,s-E* and *E,s-Z* exhibit similar stabilities. Nevertheless, the presence of bulkier substituents at the *N'* atom causes larger differences between these configurations (compare with models for compounds **7** and **8** of series III, see below). Concerning the most stable conformers around the glycosidic bond, these models also show two minima around 60° and 240° and an energy maximum close to 150°.

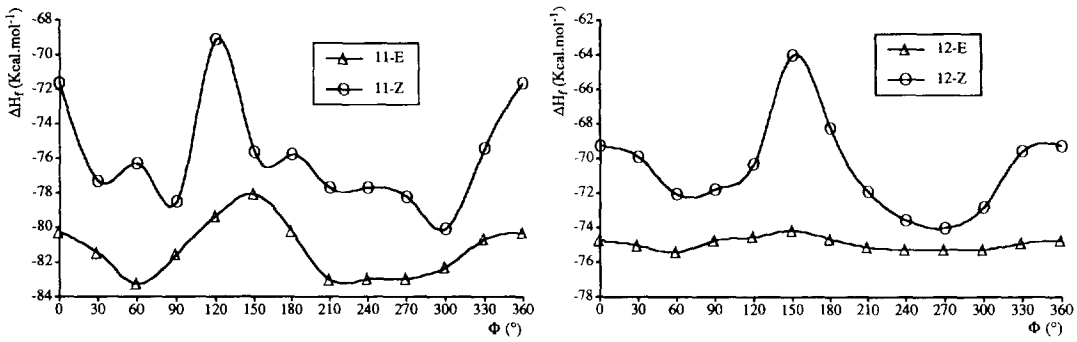


Figure 3. Plots of heats of formation *versus* the dihedral angle Φ for the conformational spectrum of model compounds **11** and **12**

NOE experiments at room temperature have been performed for compounds **1** and **2** (Fig. 5). In particular, irradiation of the amidine methyl group [MeC=N] enhanced the intensity of H-1 (8-11%) and viceversa (6-8%). This fact together with the absence of NOE effects between that methyl group and H-2 suggest the *E* configuration at the double bond as well as a torsion angle in the range $210° < \Phi < 270°$ as found in models **11-13** and rule out the alternative conformation having a dihedral angle in the range $30° < \Phi < 90°$.

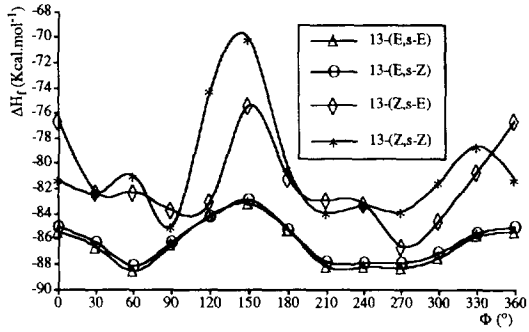


Figure 4. Plots of heats of formation *versus* the dihedral angle Φ for the conformational spectrum of model compound **13**

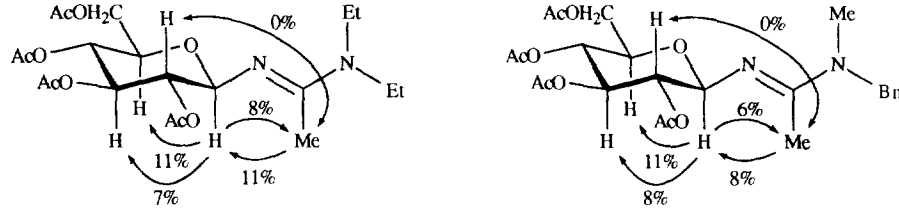
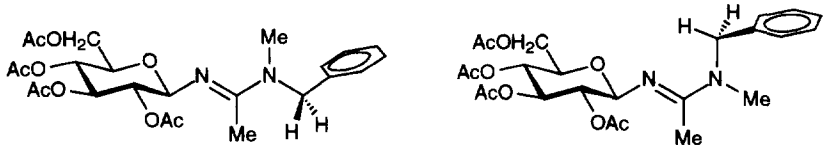


Figure 5. Selected NOEs for compounds **1** and **2**

Low-temperature ^1H- and ^{13}C-NMR experiments for compound **1** display four methylene protons or four carbon signals for ethyl groups (Tables 1-3). Compound **2** exists as a two-isomer mixture in a 57:43 ratio in $CDCl_3$ at 245K, due to restricted rotation around the C-N amidine bond. Each rotamer exhibits small

differences in the chemical shifts of sugar protons, while the greater differences are observed for the diastereotopic methylene protons (see Table 2). It is possible a conformation in the *E,s-Z* configuration (minor isomer) in which the anisotropy originated by the double bond C=N clearly affects the chemical shifts of these methylene protons ($\Delta\delta$ = 1.87 ppm). In this context, the resonance at 5.65 ppm can be attributed to the proton in the plane of the C=N bond (deshielded region) in which it experiences a greater deshielding than the other proton at 3.78 ppm in the out-of-plane region (shielded region).[22] This anisotropic effect is not possible in an *E,s-E* disposition (major isomer) in which the methylene protons show more similar chemical shifts ($\Delta\delta$ = 0.21 ppm) (Figure 6). These shift differences diminished in pyridine-d_5, presumably by masking the anisotropy of the C=N bond by interaction with the aromatic ring current of the solvent. The uncommon anisotropic effect of imines contrasts with the well-known effects observed with carbonyl groups (*e.g.* in amides).[18,22] As previously mentioned, semiempirical calculations on model **13** also agree with the stereostructures *E,s-E* and *E,s-Z* assigned to the major and minor isomers, respectively.



2-(*E, s-E*) **2**-(*E, s-Z*)

Fig. 6. Conformations of compound **2** in $CDCl_3$ at 245K

Table 1. Series I: ^{13}C-NMR chemical shifts (δ, ppm) for compounds **1-3**

Comp.	T (K)	C-1	C-2	C-3	C-4	C-5	C-6	C=N	=C-*C*	*N*-alkyl α-CH_2	α-CH_3	β-CH_2	β-CH_3	γ-CH_2
1[a]	225	88.07	73.95	73.59	69.27	72.81	63.14	162.17	13.59	43.03 41.62			14.81 12.33	
1[b]	295	88.33	73.70	73.70	69.12	73.04	62.70	161.55	13.45	42.27			13.47	
2[b]	295	88.24	73.55	73.59	69.94	73.00	62.53	162.92	13.75	52.75	36.13			
3[b]	295	94.29	73.14	73.42	68.75	73.31	62.43	155.43		50.05 42.90		26.36 25.05		24.48

[a] $(CD_3)_2CO$. [b] $CDCl_3$.

Table 2. Series I: ^{1}H-NMR chemical shifts (δ, ppm) for compounds **1-3**

Comp.	T (K)	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	N=C-Me	*N*-alkyl Me	CH_2
1[a]	295	4.78d	5.00t	5.27t	5.00t	3.95ddd	4.20dd	4.04dd	2.0-1.9	1.05t	3.48dq, 3.21dq
1[a]	225	4.85d	4.97t	5.32t	4.97t	4.02dd	4.18dd	3.95d	2.0-1.9	1.05t 0.92t	3.30dq, 3.21dq 3.59dq, 3.01dq
1[b]	295	4.68d	5.09t	5.28t	5.11t	3.82ddd	4.25dd	4.11dd	1.99s	1.08t	3.6-3.4m, 3.13dq
2[b]	295	4.71d	5.15t	5.28t	5.14t	3.81ddd	4.25dd	4.14dd	1.88s	2.94s	
2(*s-E*)[b,c]	245	4.77d	5.3-5.1m	5.4-5.2m	5.3-5.1m	3.84m	4.26dd	4.15d	1.84s	3.00s	4.62d, 4.41d
2(*s-Z*)[b,c]	245	4.72bs	5.3-5.1m	5.4-5.2m	5.3-5.1m	3.84m	4.26dd	4.15m	1.80s	2.91s	5.65d, 3.78d
2[d]	295	5.05d	5.60t	5.78t	5.49t	4.2-4.0m	4.53dd	4.36dd	2.1-2.0	2.81s	5.1-4.7m, 4.6-4.3m
2(*s-E*)[d,e]	263	5.3-5.1m	5.73t	5.94t	5.62t	4.3-4.2m	4.66dd	4.43d	2.1-2.0	2.69bs	5.5-5.2m, 4.5-4.0m
2(*s-Z*)[d,e]	263	5.3-5.1m	5.73t	5.94t	5.62t	4.3-4.2m	4.66dd	4.43d	2.1-2.0	2.97bs	5.5-5.2m, 4.5-4.0m
3[b,f]	295	4.41d	4.97t	5.25t	5.14t	3.78ddd	4.25dd	4.25dd			3.4-3.1m,1.7-1.3m

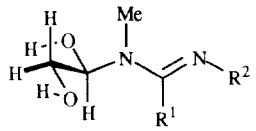
[a] $(CD_3)_2CO$. [b] $CDCl_3$. [c] *E/Z* ratio: 57/43. [d] C_5D_5N. [e] *E/Z* ratio: 53/47. [f] $\delta_{H\text{-}C=N}$ 7.39s.

Table 3. Series I: ^{1}H-NMR coupling constants (Hz) for compounds **1-3**

Comp.	T (K)	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	Alkyl J_{gem}	Alkyl J_{vic}
1[a]	295	8.2	10.5	8.8	10.0	5.5	2.4	12.0	14.0	7.0
1[a]	225	8.3	9.5	9.6	9.5	5.2	~0	11.8	14.0, 13.2	6.8, 6.7
1[b]	295	8.2	9.6	9.6	9.4	5.2	2.2	12.0	14.1	7.0
2[b]	295	8.4	9.5	9.5	10.0	5.2	2.3	12.2		
2(*s-E*)[b]	245	8.1			9.9	4.8	2.0	12.2	17.5	
2(*s-Z*)[b]	245								14.5	
2[c]	295	8.2	9.8	9.2	9.8	5.1	2.0	12.0		
3[b]	295	8.2	9.4	9.2	9.4	4.6	2.4	12.2		

[a] $(CD_3)_2CO$. [b] $CDCl_3$. [c] C_5D_5N.

Series II. Models **14** and **15** differ in the substitution pattern at the amidine carbon atom (CH_3 or H, respectively). For this class of compounds, the computational study also evidences the higher stability of *E*-isomers, while the type of conformation, *s-E* or *s-Z* do not influence markedly the energy balance and thus, the structures *s-E,E* and *s-Z,E* have similar stabilities. In full agreement with series I compounds, the models **14** and **15** exhibit a conformational minimum around the glycosidic bond for Φ ~270°. Relative minima are also located in the range 30° < Φ < 90° and a pronounced maximum for 150° < Φ < 180°.



14 $R^1 = R^2 = Me$
15 $R^1 = H$, $R^2 = Me$
16 $R^1 = Me$, $R^2 = H$
17 $R^1 = R^2 = H$

Compared with **14** and **15**, models **16** and **17**, for which the substituent at the iminic nitrogen is hydrogen, gave similar results, evidencing the scarce influence of a bulkier group on that nitrogen atom. In the model **16**, the minimum for the *s-E,E* structure is located for Φ ~270°, whereas **17** reaches the minimum for the same dihedral angle in a configuration *s-E,Z* though all the structures are close in energy (< 2 kcal/mol).

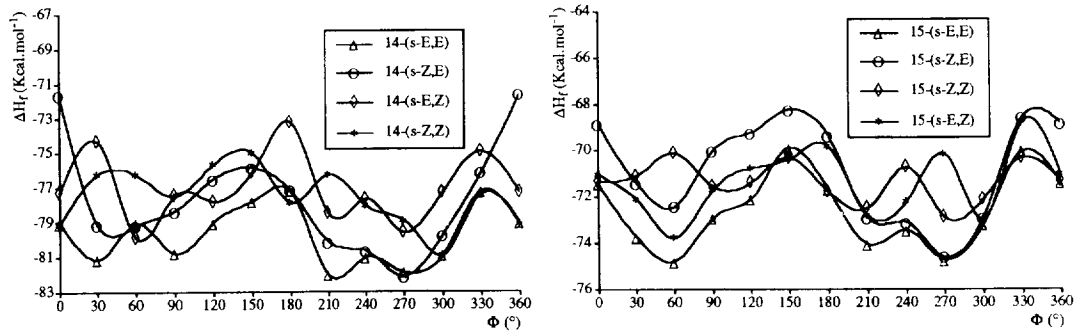


Figure 7. Plots of heats of formation *versus* the dihedral angle Φ for the conformational spectrum of model compounds **14** and **15**.

Low-temperature NMR experiments for compound **4** in $CDCl_3$ at 225 K and for **5** and **6** in acetone-d_6 at 210 and 220 K, respectively, showed one signal set indicating the existence of a single rotamer for these compounds (Tables 4, 5). NOE measurements for **4** and **5** at 295 K were also of diagnostic value in determining the configuration of these glycoamidines (Fig. 8, *vide infra*).

Table 4. Series II: ^{13}C-NMR chemical shifts (δ, ppm)[a] for compounds **4-6**

Comp.	C-1	C-2	C-3	C-4	C-5	C-6	C=N	=C-C	N-alkyl α-CH_x	N-alkyl β-CH_2	N-alkyl β-CH_3	N-alkyl γ-CH_3
4	83.42	69.02	74.03	68.46	73.16	62.00	153.11	12.20	44.76	23.27	24.58 24.49	11.36
5	83.24	68.89	73.96	68.57	73.14	61.93	155.74	12.54	51.08 44.89	24.74 23.32		11.79 11.28
6	83.37	69.06	73.68	68.21	73.51	61.82	155.51	14.90	45.14	23.17		11.41

[a] In $CDCl_3$ at 295K.

Table 5. Series II: ^{1}H-NMR chemical shifts (δ, ppm)[a] for compounds **4-6**

Comp.	H-1	H-2	H-3	H-4	H-5	H-6,6'	N=C-Me	*N*-alkyl α-CH	*N*-alkyl α-CH_2	*N*-alkyl β-CH_2	*N*-alkyl β-CH_3	*N*-alkyl γ-CH_3
4[b,c]	5.62d	5.18t	5.29t	5.08t	3.74dt	4.3-4.1m	1.88s	3.49dq	3.22ddd 3.00ddd	1.7-1.3m	1.03d 1.02d	0.82t
5[d,e]	5.57d	5.19t	5.32t	5.05t	3.95dt	4.2-4.1m	2.0-1.9s		3.34ddd 3.06ddd 3.12t	1.6-1.4m 1.49dq		0.91t 0.80t
5[b]	5.67d	5.19t	5.25t	5.09t	3.75dt	4.2-4.1m	2.1-1.8s		3.14t 3.4-2.9m	1.7-1.4m		0.91t 0.83t
6[b,f]	5.71bs	5.29t	5.33t	5.13t	3.78dt	4.21m	1.89s		3.38ddd 3.13ddd			0.88t

[a] At 295K. [b] $CDCl_3$. [c] One signal set from 295 to 225K. [d] $(CD_3)_2CO$. [e] One signal set from 295 to 210K. [f] One signal set from 295 to 220K in $(CD_3)_2CO$.

Table 6. Series II: ^{1}H-NMR coupling constants (Hz) for compounds **4-6**

Comp.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	J_{gem}	$J_{CH_2CH_2}$	$J_{CH_2CH_3}$	J_{CHCH_3}
4[a]	8.9	9.3	8.9	10.1	3.0	3.0	15.0	9.5, 5.0	7.4	6.2
5[b]	8.9	9.3	9.1	10.1	3.7	3.7	14.1	10.0, 6.6, 5.2	7.4, 7.2	
5[a]	8.8	10.0	9.3	9.3	5.0	5.0		6.9, 5.1	7.4	
6[a]	8.9	9.1	9.3	9.9	3.3	3.3		10.0, 5.4	7.4	

[a] In $CDCl_3$ at 295K. [b] In $(CD_3)_2CO$ at 295K.

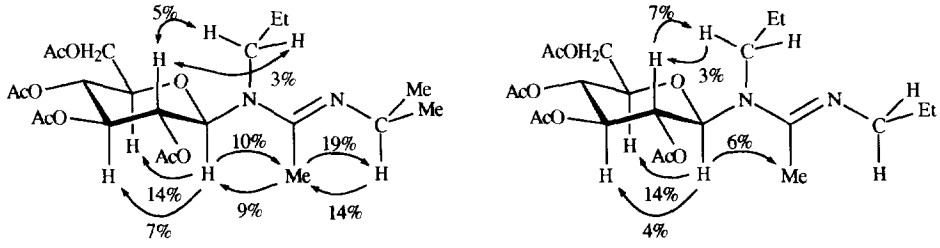


Figure 8. Selected NOEs for compounds **4** and **5**

Irradiation of the amidine methyl group, [-N-C(CH_3)=N-], in compound **4** enhanced the NOE intensity of H-1 (9%), while the enhancement for H-2 lies in the range 1-2% only. Moreover, a strong NOE effect (19%) is observed between the amidine methyl and the CH proton of the isopropyl group. These observations are consistent with configurations *s-E* and *E* for N-C and C=N bonds of amidine, respectively, and a torsional angle of Φ ~270° as calculated for the model **14**. On the contrary, values of Φ in the range 30-90° are not consistent with NOEs observed. With such a torsional angle (Φ ~270°), either in *s-E* or *s-Z* conformations, H-1 and the C=N bond are almost coplanar with the anomeric proton being deshielded strongly.[18,22] However, it is

expected the *s-Z* conformer experience the greater deshielding and, if present in solution, the anomeric proton would resonate at lower field than that of *s-E* conformer (Figure 9).

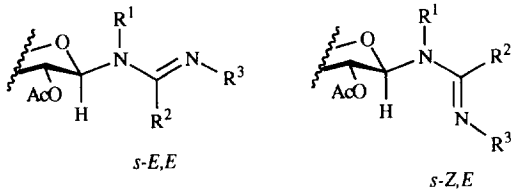
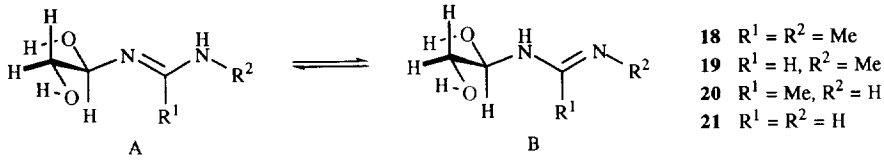


Figure 9

Series III. Semiempirical calculations have been accomplished for all the possible stereostructures of both tautomers, A and B, of models **18-21**. Figure 10 depicts this situation for compounds **18** and **19**. In the case of A, minima are reached for Φ values around 60° and 240° and maxima close to 150°, being *E,s-E* the most stable configuration anew, in accordance with series I models. Similarly, tautomers B give results comparable to those of series II in which the *s-E,E* is the most stable structure and the conformational minimum is found around 270°.



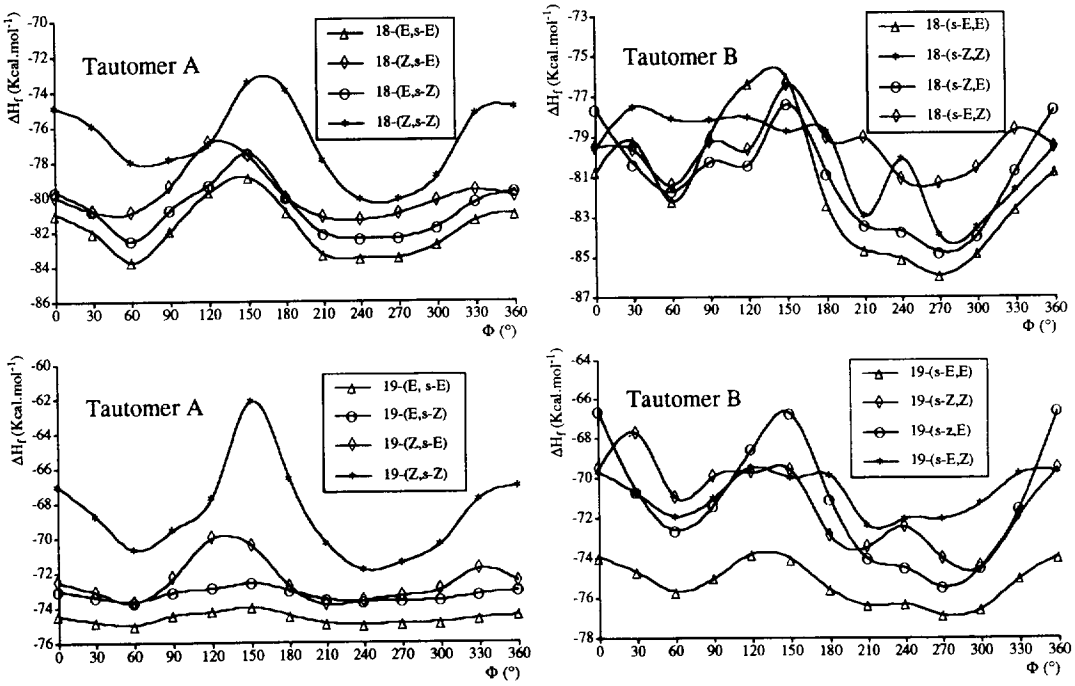


Figure 10. Plots of ΔH_f *versus* the dihedral angle Φ for the possible configurations of tautomers of **18-19**.

Figure 11 shows that for the *N'*-alkylsubstituted models **18** and **19**, calculations predict that the most stable stereostructures have the *s-E,E* configuration (tautomer B). In compounds **20** and **21** the double bond is vicinal to the anomeric center and *E*-isomers (tautomer A) are the most stable compounds.

NMR data have proven to be of benefit for the tautomeric assignment of compounds **7-10** (Tables 7-9). Nevertheless, these data clearly suggest that, in solution, compounds **7** and **8** exist as the tautomer A whereas **9** and **10** exist in the tautomeric form B. In series I compounds, H-1 resonates to upper fields (4.41-4.71 ppm, $CDCl_3$, room temperature) than those of series II (5.62-5.71 ppm). Series III compounds exhibit an intermediate behavior depending on the substituents at the *N'* nitrogen atom. With alkyl groups (compounds **7** and **8**) δ_{H-1} is similar to that of series I compounds (4.39, 4.80 ppm in $CDCl_3$), whereas aromatic substituents (compounds **9** and **10**) induce δ_{H-1} (5.50, 5.52 ppm) comparable to those of series II compounds.[19] Moreover, H-1 appears as doublet in **7** and **8**, and as triplet in **9** and **10** (Table 7). Similar conclusions can be extracted from the shift of C-1, and thus in compound **7** that carbon resonates at 88.09 ppm, which is coincidental with that of **1** an **2** (δ_{C-1} ~88 ppm), while in the formamidine **8** C-1 appears at 94.34 ppm, identical to its analogous carbon in **3** (δ_{C-1} ~94 ppm). As expected, the position of the double bond agrees with that of simple amidines in which the electronic character of substituents fixes its location. In compounds **9** and **10** the iminic double bond is conjugated with aryl groups as in *N*-alkyl-*N'*-arylamidines,[9a] while in **7** and **8** that nitrogen is linked to the more electronegative anomeric carbon atom.[9c]

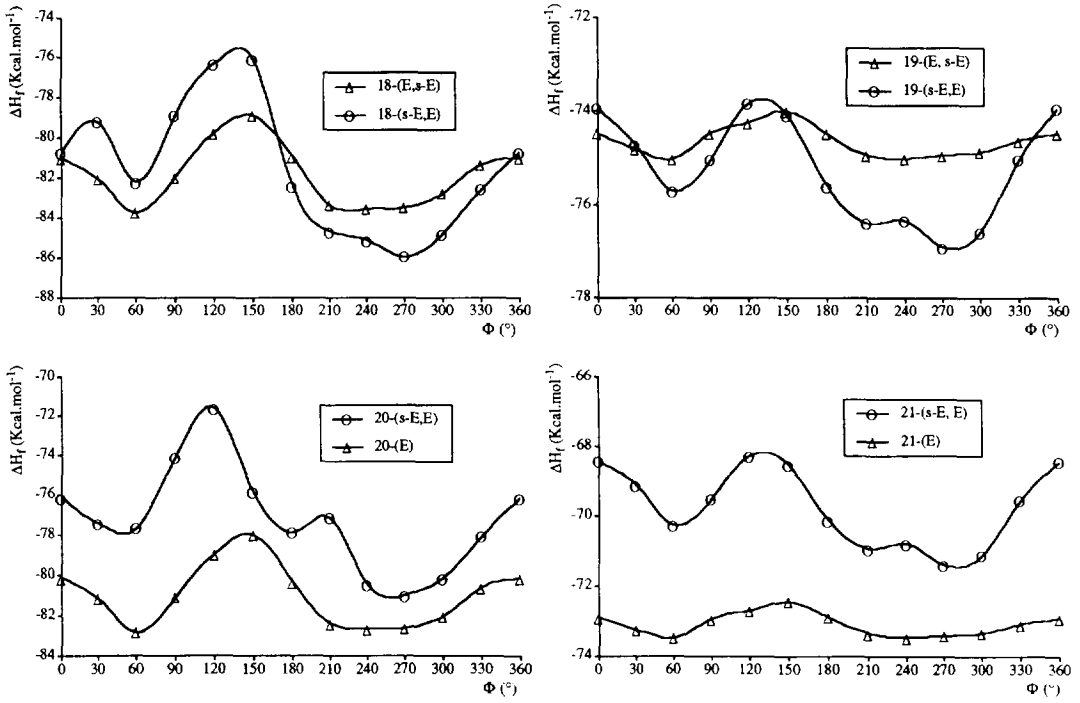


Figure 11. Plots of ΔH_f *versus* the dihedral angle Φ for the conformers of model compounds **18-21**.

NOEs are also useful for the assignment of the stereoconfiguration of glycoamidines of this series (Fig. 12). In compound **8**, the different enhancements of H-1 (20%) and H-2 (1%) upon irradiation of the formamidino proton (CH=) are indicative of an *E* configuration around the double bond and a torsional angle compatible with those of model compounds **18** and **19** (θ ~270°).

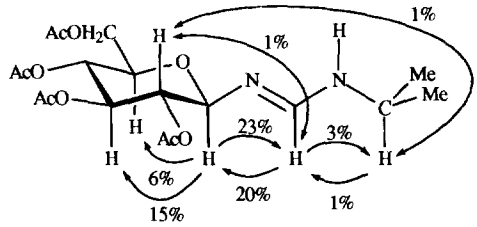


Figure 12. Selected NOEs for compound **8**

Table 7. Series III: ^{1}H-NMR chemical shifts (δ, ppm) for compounds **7-10**.

											N-alkyl	
Comp.	T (K)	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	NH	N=C-*R*	α-CH_x	CH_3
7*(s-E)*[a,b]	295	4.86m	5.01t	5.27t	5.00t	3.94m	4.20dd	4.07dd	4.3-4.1m	2.1-1.8s	4.60d	
7*(s-Z)*[a,b]	295	4.86m	5.1-4.9m	5.15t	5.1-4.9m	4.0-3.9m	------4.2-3.9m------		4.3-4.1m	2.1-1.8s	4.60d	
7[c]	295	4.8-4.4m	5.10t	5.28t	5.14t	3.81d	4.25dd	4.13dd	4.8-4.4m	2.1-1.9s	4.8-4.4m 4.3-4.0m	
7[d]	295	5.04d	5.53t	5.70t	5.41t	4.1-4.0m	4.47dd	4.32dd	4.34d	2.11s	5.1-4.5m	
8[a]	295	4.49d	4.92dd	5.27t	5.04t	3.92ddd	4.22dd	4.04dd	6.17dd	7.55s	4.0-3.8m	1.13d 1.08d
8[a]	240	4.50d	4.94t	5.29t	5.03t	4.1-3.8m	4.20dd	4.01d	6.43dd	7.55d	4.0-3.8m	1.12d 1.05d
8[c]	295	4.39d	5.01t	5.25t	5.13t	3.79ddd	4.25dd	4.13dd	4.63bs	7.48s	4.3-4.0m	1.16d
8*(s-E)*[c,e]	273	4.39d	5.08t	5.28t	5.18t	3.82d	4.26dd	4.14dd	4.77m	7.50s	4.3-4.0m	1.15d 1.12d
8*(s-Z)*[c,e]	273	4.5-4.3m	4.94t	------5.4-	5.0m-----	3.9-3.7m	------4.3-	4.0m-----	5.4-5.0m	7.50s	4.3-4.0m	1.3-1.1m
9[a]	295	5.50bs	4.97t	5.34t	5.09t	3.9-3.8m	4.32dd	4.11dd	5.2-4.8bs	1.77s		3.78s
9[a]	250	5.53t	5.03t	5.38t	5.16t	3.95d	4.39d	4.11d	5.30d	1.78s		
10[a]	295	5.52bs	4.98t	5.35t	5.09t	3.9-3.8m	4.32dd	4.12dd	5.4-5.2m	1.76s		
10[a,f]	250	5.47t	4.94t	5.30t	5.08t	3.85d	4.31dd	4.03d	5.36d	1.78s		

[a] $(CD_3)_2CO$. [b] *E/Z* ratio: 66/34. [c] $CDCl_3$. [d] C_5D_5N. [e] *E/Z* ratio: 78/22. [f] One signal from 285 to 230K.

Table 8. Series III: ^{1}H-NMR coupling constants (Hz) for compounds **7-10**

											Alkyl	
Comp.	T (K)	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{NH,=CH}$	$J_{NH,-CH-}$	J_{gem}	J_{vic}
7*(s-E)*[a,b]	295	9.3	9.9	9.1	9.9	5.4	2.5	12.1			14.3	
7*(s-Z)*[a,b]	295		9.5	9.5								
7[c]	295	8.5	9.9	9.1	9.9	5.0	2.3	12.0				
7[d]	295	8.1	8.7	9.5	9.9	4.8		12.3			14.3	
8[a]	295	8.3	9.9	9.5	9.9	5.0	2.1	12.2		~3		6.6, 6.4
8[a]	240	8.3	9.7	9.7	9.5	5.3	~0	12.3	4.0	7.1		6.6, 6.3
8[c]	295	8.0	9.0	9.4	9.4	4.4	2.1	12.3				6.0
8*(s-E)*[c,e]	273	8.1	9.5	9.5	9.5	3.7	~0	12.4		~6		6.9, 6.5
8*(s-Z)*[c,e]	273	~8	~8									6.8
9[c]	295	9.5	9.5	9.5	9.6	4.4	2.0	12.3				
9[c]	250	9.2	9.2	9.7	9.7			12.2				
10[c,f]	295	8.0	9.5	9.5	~10	4.4	1.9	12.5				
10[c,f]	250	9.0	9.5	9.5	~9	3.4	~0	12.4				

[a] $(CD_3)_2CO$. [b] E/Z ratio 88:72. [c] $CDCl_3$. [d] C_5D_5N. [e] E/Z ratio 66:34. [f] One signal set was visualized until 230K.

Table 9. Series III; ^{13}C-NMR chemical shifts (δ, ppm) for compounds **7-10**

									N-alkyl			
Comp.	C-1	C-2	C-3	C-4	C-5	C-6	C=N	=C-*C*	α-CH_2	α-CH	β-CH_3	O-CH_3
7[a,b]	88.09	73.47	73.47	68.76	73.11	62.41	160.34	17.30	45.08			
7[b,c]	88.51	74.53	74.42	69.70	73.36	62.99	162.23	16.87	45.08			
7[b,d]	88.52	74.59	74.46	70.03	73.64	63.39	162.52	17.01	44.76			
8[a,b]	94.39	72.64	73.24	68.48	73.06	62.17	152.29			47.06	23.76, 22,21	
8(*s-E*)[a,e]	94.75	72.32	73.00	68.13	72.88	62.01	152.43			42.00	22.11, 21.83	
8(*s-Z*)[a,e]	94.75	72.32	73.00	68.13	72.88	62.01	152.43			42.00	24.17, 23.78	
9[a,b]	79.48	70.97	72.90	68.27	72.90	61.78	143.24	17.24				55.31
10[a,b]	79.29	70.83	72.80	68.18	72.80	61.69	150.00	17.00				

[a] In $CDCl_3$. [b]At 295K. [c]In C_5D_5N. [d]In $(CD_3)_2CO$. [e]At 273K.

The *N'*-alkylamidines **7** (acetone-d_6, 295K) and **8** ($CDCl_3$, 273K) show two signal sets in their NMR spectra. These isomers, however, should be considered rotamers around the C-N amidine bond and not tautomers, because chemicals shifts for H-1 are quite similar in both isomers and comparable to those of series I. Likewise and according to theoretical calculations, the *s-E* conformation attributed to the major isomer at the C-N amidine bond is stabilized over the *s-Z* disposition (Figure 10). It should be noted that systems in which the -CH-NH- moiety possesses a certain degree of double bond such as formamides and thioformamides,[18] the coupling constant between such protons is greater in a *trans* disposition. Thus in compound **8**, the *s-E* conformation is supported by its $J_{NH,CH=}$ coupling constant (6 Hz), greater than that of minor isomer for which the coupling could not be accurately measured. Similarly, spectroscopic data for compound **7** suggest a large amount of the *s-E* rotamer. Consequently the preponderant isomer of compounds **7** and **8** should exist in an *E,s-E* arrangement, whereas the stereoconfiguration of the minor one should be *E,s-Z*.

No duplication of signals was observed for compounds **9** and **10** at low temperature (230 K, $CDCl_3$) and it was impossible to obtain conformational information from NOE experiments. Nevertheless, chemical shifts for H-1 protons correlate with those of series II compounds. Also, the $J_{H\text{-}1,NH}$ couplings (9.2 and 9.0 Hz, respectively) could be measured at low temperature and such values indicate an *anti* disposition between both protons and a dihedral angle close to those of series II compounds. The *s-E,E* arrangement is supported by the semiempirical calculations of compounds **18** and **19** described above. According to our predictions for series II compounds, the anomeric proton in the *s-Z,E* configuration would resonate at lower fields.

In conclusion, the following points should be noted:

a) For glycoamidines whose iminic nitrogen atom is directly linked to the anomeric center (compounds **1-3**, **7**, and **8**), two rotamer populations around the C-N amidine bond have been observed with a larger population of the *s-E* rotamer.

b) Alternatively, when the glycosidic carbon atom binds to an amine nitrogen (compounds **4-6**, **9**, and **10**) the *s-E* rotamer was exclusively observed.

c) In *N,N'*-disubstituted glycoamidines, the imine function is bound to the sugar framework with *N'*-alkyl groups (**7** and **8**), whilst the latter nitrogen becomes iminic with aryl substituents (**9** and **10**).

d) Chemical shifts of H-1 protons (and C-1 atoms) provide information concerning the assignment of tautomers, because they resonate to upper fields when an imine moiety joins the anomeric center and to lower ones with amine groups.

e) NOE effects are of diagnostic value for assigning the type of isomerism around the C=N amidine bond as well as the conformation around the glycosidic bond. Moreover, semiempirical calculations on representative aglycon models corroborate the preferential torsion angles.

EXPERIMENTAL

The synthesis of compounds **1-10** has been previously described.[19] ^{1}H- (200 MHz) and ^{13}C-NMR (50.3 MHz) spectra were recorded on a Bruker AC 200-E spectrometer. In addition, ^{1}H-NMR spectra of compound **2** in $CDCl_3$ were also recorded at 400 MHz with a Bruker 400 AC/PC. Assignments were confirmed by homo- and hetero-nuclear double-resonance, and DEPT experiments. TMS was used as the internal standard (δ = 0.00 ppm) and all J values are given in Hz. Deuterated solvents (99.9% D) were purchased from Cambridge Isotope Laboratories (Cambridge, MA). Geometry optimizations and heats of formation were estimated using the semiempirical method[20,21] MNDO-PM3 (Modified Neglected of Diatomic Overlap-Parametric Method 3),[21] based on the NDDO approach (Neglect of Diatomic Differential Overlap) from MOPAC programs[23] 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.

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