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ALDOSE–AMINOGUANIDINE CONDENSATION PRODUCTS: SYNTHESES AND N.M.R. STUDIES

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ABSTRACT

The condensation products of aldoses with aminoguanidine exist in aqueous solution at pH 6 as cyclic pyranosylaminoguanidines with the protonated aminoguanidine substituent at C-1 equatorial, and at pH 12 and in methyl sulfoxide as acyclic *E*-carboximidamidehydrazones. The cyclic isomers are present exclusively when mineral acid salts of the condensation products are dissolved in methyl sulfoxide. The sites of protonation and tautomerism at the aminoguanidine moiety have been studied by ^{1}H-, ^{13}C-, and ^{15}N-n.m.r. methods, and mechanisms for the pH-dependent cyclic–acyclic interconversion are discussed.

INTRODUCTION

The products of reaction of monosaccharides with hydrazine derivatives are generally crystalline and frequently used for characterisation and identification[1]. Such products derived from biologically active hydrazine derivatives often show decreased toxicity and/or increased solubility in water compared to the parent hydrazines.

Derivatives of carbohydrates obtained by reaction with substituted hydrazines have been studied in detail[2,3] and by n.m.r. spectroscopy[4–9]. The structures of the derivatives of unsubstituted hydrazones[10–13], thiosemicarbazones[14–17] semicarbazones[18–23], methyl dithiocarbazonates[24], carboximidamidehydrazones ("guanylhydrazones")[25,26], nitroguanylhydrazones[27], arylsulfonylhydrazones[28–31], *N*-methylbenzthiazolylhydrazones[32], phosphorylhydrazones[33] and thioacylhydrazones[34] are less well known. The ring-chain tautomerism of aldose hydrazones[35], acyl-

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hydrazones[4,36], and thiosemicarbazones[37] have been investigated by ^1H- and ^{13}C-n.m.r. spectroscopy.

Aminoguanidine (hydrazinecarboximidamide, **1**) and its derivatives are highly reactive[38] and are versatile starting materials for heterocyclic syntheses[39]. We now report on the products obtained by the reaction of monosaccharides with **1**. The reaction of **1** · HCl with D-glucose, D-galactose, and lactose was first described by Wolff[25], but the structures of the products were not investigated. Such condensation products and chromogenic compounds derived therefrom have been utilised for the detection of sugars in solution[40] and in chromatography[41]. The product of reaction of **1** with D-mannose possesses interesting immunological properties[42] and bis(carboximidamidehydrazones) of some uloses are active against *Botrytis allii*[43].

RESULTS AND DISCUSSION

L-Arabinose, D-glucose, D-galactose, and D-mannose reacted rapidly with aminoguanidine salts (HCl and HNO_3) at 100° in concentrated solutions in water or

TABLE I

ALDOSE CARBOXIMIDAMIDEHYDRAZONES

Compound	*M.p. (degrees)*	*Yield (%)*	$[\alpha]_D^a$ *(degrees)*	*Formula*	*Calc. Found*			
					C	*H*	*Cl*	*N*
2	135–136	96[b]	−27	$C_6H_{14}N_4O_4$	34.95	6.84	—	27.17
					35.34	6.87		26.99
2·HCl	193–195	88[b]	+23	$C_6H_{15}ClN_4O_4$	29.67	6.18	14.63	23.08
					30.19	6.39	14.41	22.39
2·HNO_3	166–167	90[c]	+5	$C_6H_{15}N_5O_7$	26.77	5.62	—	26.01
					26.97	6.21		25.93
3	glass	98	−1.5	$C_7H_{16}N_4O_5$	35.60	6.83	—	23.72
					34.93	5.99		23.70
3·HCl	174[d]	67[b]	−16	$C_7H_{17}ClN_4O_5$	30.82	6.96	13.01	20.55
					30.95	6.90	13.06	20.70
3·HNO_3	185–186	89[b]	−12	$C_7H_{17}N_5O_8$	28.09	5.73	—	23.40
					28.51	5.98		23.17
4	162 (dec.)	81[b]	0	$C_7H_{16}N_4O_5$	35.60	6.83	—	23.72
					36.13	7.21		23.47
4·HCl	160	92[b]	+7	$C_7H_{17}ClN_4O_5$	30.82	6.96	13.01	20.55
					30.90	7.10	13.04	20.60
4·HNO_3	156–157	90[b]	−9	$C_7H_{17}N_5O_8$	28.09	5.73	—	23.40
					28.54	5.91		22.77
5	167–168	92[b]	+4	$C_7H_{16}N_4O_5$	35.60	6.83	—	23.72
					36.12	6.84		22.98
5·HCl	glass	quant.	−41	$C_7H_{17}ClN_4O_5$			13.01	20.55
							13.12	20.67
5·HNO_3	glass	quant.	−39	$C_7H_{17}N_5O_8$	28.09	5.73	—	23.40
					28.18	5.60		22.96

[a]Water (*c* 1) at 20–24°. [b]From ethanol–water. [c]From ethanol. [d]Lit.[25] m.p. 165°.

TABLE II

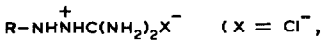
ACETYLATED ALDOSE CARBOXIMIDAMIDOHYDRAZONES

Compound	*M.p. (degrees)*	*Yield (% recryst.)*	$[\alpha]_D^a$ *(degrees)*	*Formula*	*Calc. Found*			
					C	*H*	*Cl*	*N*
6·HCl	152–153 (dec.)	87[b]	+70	$C_{14}H_{23}ClN_4O_8$	40.93 40.66	5.64 5.80	8.63 8.68	13.64 13.11
6·HNO_3	161–162 (dec.)	48[c]	+67	$C_{14}H_{23}N_5O_{11}$	38.44 38.67	5.30 5.65	—	16.01 16.01
7·HCl	glass	86	—	$C_{17}H_{27}ClN_4O_{10}$	42.28 41.94	5.64 5.34	7.34 7.28	11.60 10.86
7·HNO_3	139–142 (dec.)	82[b]	+86	$C_{17}H_{27}N_5O_{13}$	40.08 40.21	5.34 5.73	—	13.75 13.70
8·HCl	178–182	86[c]	+85	$C_{17}H_{27}ClN_4O_{10}$	42.28 42.11	5.64 5.70	7.34 7.36	11.60 11.30
8·HNO_3	175–176	79[c]	+91	$C_{17}H_{27}N_5O_{13}$	40.08 40.61	5.34 5.39	—	13.75 13.47

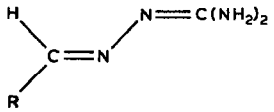
[a]Chloroform (*c* 1) at 21–24°. [b]From 2-propanol. [c]From ethanol.

aqueous ethanol to give the products listed in Table I. With the exception of those from the salts of **5**, the products were non-hygroscopic stable compounds although some were claimed[25] to be hygroscopic. They were homogeneous in t.l.c. and reacted with sulfuric acid to give bluish spots (*cf.* ref. 41). The free bases **2**–**5**, readily obtained by ion-exchange, were very stable and, like **1**, were strong bases in aqueous solution. The condensation products **6**–**8**·HX (X = Cl, NO_3) were obtained by the reactions of acetylated *aldehydo*-L-arabinose, -D-glucose, and D-galactose, respectively, with **1**·HCl or **1**·HNO_3 (Table II). These salts were soluble in water and chloroform, but attempts to prepare the free bases by addition of 1 mol of $NaHCO_3$ to aqueous solutions caused rapid decomposition.

The condensation products of monosaccharides with amino compounds are generally discussed[2,3] in terms of acyclic and cyclic forms often present as equilibrium mixtures in solution and, due to the presence of basic nitrogen atom(s), a strong influence of pH on this equilibrium would be anticipated. Haas *et al.*[21] established, using polarography, that aldose hydrazones exist mainly in cyclic forms in aqueous media at low pH and this has been confirmed by ^{13}C-n.m.r. studies[35]. Similar phenomena have been observed[44] with aldose oximes, hydrazones, and carboximidamidehydrazones. ^1H- and ^{13}C-n.m.r. data reflect the structures of such derivatives in solution. Thus, for aldose oximes, the signal of the azomethine (CH=N) proton is at ~7.4 p.p.m. in the *E*-isomer and at 6.7–6.9 p.p.m. in the *Z*-form. The chemical shifts for the OH-signals of oximes are also useful for differentiating *E*- and *Z*-isomers when measurements are performed under conditions of slow exchange (*e.g.*, in methyl sulfoxide)[4,5]. The pyranoid forms are readily identified by the signals at ~4 p.p.m. for H-1, the values depending on the anomeric configura-



2·HX R = α-L-arabinopyranosyl
3·HX R = β-D-glucopyranosyl
4·HX R = β-D-galactopyranosyl
5·HX R = β-D-mannopyranosyl



2 R = α-L-arabinopyranosyl
3 R = β-D-glucopyranosyl
4 R = β-D-galactopyranosyl
5 R = β-D-mannopyranosyl
6 R = L-*arabino*-1,2,3,4-tetra-acetoxybutyl
7 R = D-*gluco*-1,2,3,4,5-penta-acetoxypentyl
8 R = D-*galacto*-1,2,3,4,5-penta-acetoxypentyl

tion and the solvent[4,5,8,13,37,45,46]. For aldose *O*-methyl oximes, for instance, the signal of the sp^2-hybridised C-1 occurs at 151–153 p.p.m. for *E*-isomers and at 153–155 p.p.m. for *Z*-isomers[47]. For acyclic hydrazones and substituted hydrazones[6,35,37], the signals for C-1 are in the range 140–150 p.p.m., but the difference between *E*- and *Z*-isomers is insignificant. The $J_{C\text{-}1,H\text{-}1}$ value is a potentially useful parameter for assigning *E*/*Z* configurations in aldose derivatives. A difference of 14 Hz was reported[48] for the $^1J_{C,H}$ values of non-carbohydrate *E*- and *Z*-oximes, and values of 163.2 and 175.3 Hz were measured[44] for the *E*- and *Z*-isomers, respectively, for L-arabinose oxime in solution in D_2O. Pyranosylamine structures are easily recognised by resonances in the range 80–95 p.p.m. characteristic for anomeric carbons[4,5,9,37].

The ^{1}H-n.m.r. spectra of solutions of the carboximidamidehydrazones **2–5** in D_2O were pH-dependent. Thus, at pH 6, **4** existed exclusively in the β-pyranosylaminoguanidine form, as evidenced by the signal for H-1 at 4.1 p.p.m. (d, $J_{1,2}$ 11.2 Hz) and the absence of any signal at ~5 p.p.m. At high pH, this doublet was replaced by one at 7.5 p.p.m. characteristic for H-1 in the acyclic hydrazone form. The pH-dependence of the cyclic:acyclic ratio (determined from the integrated intensities of the two doublets) for solutions of **4** in D_2O is shown in Fig. 1. At pH 8, only the β-pyranoid form was present and at pH >12 only the acyclic form was detected. A similar situation was found for **2**, **3**, and **5**. The chemical shifts of the signals for H-1 and the $J_{1,2}$ and $J_{2,3}$ values (Table III) establish the α-L($^4C_1$) structure for **2** and the β-D($^4C_1$) structures for **3** and **4** at pH ~6. The chemical shift of the

TABLE III

^{1}H-N.M.R. DATA (D_2O)

Compound	*pH*	*Form*	*Chemical shifts[a] and coupling constants[b]*								*Other*
			H-1 ($J_{1,2}$)	*H-2* ($J_{2,3}$)	*H-3* ($J_{3,4}$)	*H-4*	*H-5a* ($J_{4,5a}$)	*H-5b* ($J_{4,5b}$)	*H-6a* ($J_{5,6a}$)	*H-6b* ($J_{5,6b}$)	
2	6	α-L($^4C_1$)	4.02 (8.6)	3.55 (~9)	3.6–4.0				—	—	
	12	*E*	7.50 (5.6)	4.39 (2.7)	3.55–3.75				—	—	6.87 ($J_{1,2}$ ~4 Hz; *Z*-isomer ~2%)
3	6	β-D($^4C_1$)	4.14 (9.2)	3.32 (9.2)	3.4–3.6			—	3.92 (2.0)	3.72 (5.4)	$J_{6a,6b}$ 12.2 Hz
	12	*E*	7.45 (7.3)	4.33 (6.0)	3.5–3.9			—	3.5–3.9		6.78 ($J_{1,2}$ ~4 Hz; *Z*-isomer 2%)
4	6	β-D($^4C_1$)	4.12 (11.2)	3.55 (12.1)	3.72–3.82		3.95	—	3.70 (~1)	3.71 (4.2)	$J_{6a,6b}$ 12.1 Hz
	12	*E*	7.53 (5.1)	4.49 (2.7)	3.88 (9.2)	3.65–3.80	3.99	—	3.65–3.80		6.90 ($J_{1,2}$ ~4 Hz; *Z*-isomer ~2%)
5	6	β-D($^4C_1$)	4.33 (~1)		3.3–4.1				3.3–4.1		
	12	*E*	7.54 (5.4)	4.30 (8.0)	3.93 (1.2)	3.62–3.87		—	3.62–3.87		
6·HNO_3	6	*E*	7.42 (3.6)	5.74 (2.9)	5.66 (7.8)	5.36	4.41 (3.0)	4.29 (4.8)	—	—	$J_{5a,5b}$ 12.6 Hz
7·HNO_3	6	*E*	7.40 (3.9)	5.65	5.5		5.40	—	4.33 (5.0)	4.14 (6.8)	$J_{6a,6b}$ 13.1 Hz
8·HNO_3	6	*E*	7.44 (5.1)	5.61 (6.5)	5.68 (2.0)	5.52	5.20 (8.5)	—	4.31 (2.4)	4.24 (4.3)	$J_{6a,6b}$ 13.0 Hz

[a]In p.p.m. from sodium trimethylsilylpropanoate. [b]In Hz.

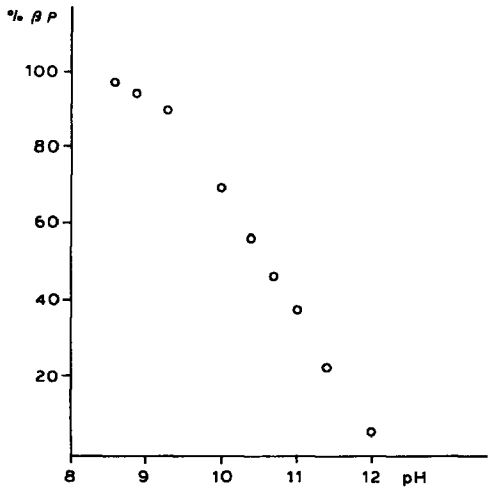


Fig. 1. Percentage of the β-D-pyranosylaminoguanidine form (*βp*) of **4** as a function of the pH. Solutions of **4** were prepared in glycine–NaOH buffer in D_2O, and the pH values refer to direct meter readings.

TABLE IV

^{13}C-N.M.R. DATA (D_2O)

Compound	*pH*	*Form*	*Chemical shifts*[a]						
			C-1 ($J_{C,H}$)	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	C_g
2	6	α-L($^4C_1$)	90.50 (154.5)	73.27	68.82[b]	68.32[b]	67.66	—	158.86
	12	*E*	150.22 (159.0)	72.57;71.39;70.74			63.09	—	161.63
3	6	β-D($^4C_1$)	89.52 (155.8)	70.62[c]	77.00[b]	69.74[c]	76.46[b]	6.19	158.43
	12	*E*	150.57 (161.9)	72.97	71.94	71.81	71.77	6.15	162.73
4	6	β-D($^4C_1$)	89.22 (155.0)	68.10[b]	72.69	67.30[b]	75.31	60.60	157.69
	12	*E*	149.69 (163.4)	70.47	69.67	69.55	68.89	62.53	160.68
5	6	β-D($^4C_1$)	89.67 (156.9)	72.21	75.91	69.67	79.51	63.83	160.76
	12	*E*	154.55 (162.2)	74.62;74.19 (2×);73.47				65.74	163.70
6·HNO_3	6	*E*	145.23 (172.1)	70.40;69.52;68.85			62.20	—	155.47
7·HNO_3	6	*E*	144.98 (170.9)	70.00	68.62;68.26 (2×)			62.58	155.34
8·HNO_3	6	*E*	144.50 (170.9)	71.70	69.33;69.00;68.82			61.95	155.47

[a]In p.p.m., from external Me_4Si. [b,c]Assignments may be interchanged pairwise.

TABLE V

^{1}H-N.M.R. DATA [$(CD_3)_2SO$]

Compound	*Form*	*Chemical shifts[a] and coupling constants[b]*															
		H-1 $J_{1,2}$	*H-2* $J_{2,3}$	*H-3* $J_{3,4}$	*H-4*	*H-5a* $J_{4,5a}$	*H-5b* $J_{4,5b}$	*H-6a* $J_{5,6a}$	*H-6b* $J_{5,6b}$	*HO-2* $J_{2,OH}$	*HO-3* $J_{3,OH}$	*HO-4* $J_{4,OH}$	*HO-5* $J_{5,OH}$	*HO-6* $J_{6,OH}$	*N''-H*	*N'-H*	*NH_2*
2·HNO_3	α-L($^4C_1$)	3.65 (8.5)	3.25–3.37		3.62	3.71 (2.4)	3.45 (~1)	—	—	4.88[c] (2.5)	4.86[c] (~1)	4.61 (3.5)	—	—	5.96 (8.5)	8.86	7.49[d] 6.80[d]
2	*E*[e]	7.34 (4.9)	4.28 (2.5)	3.39 (10.0)	3.40–3.63			—	—	5.7[d];5.1[d];4.5[d]							
3·HNO_3	β-D($^4C_1$)	3.80 (8.8)	3.02 (8.5)	3.23 (8.5)	3.07	3.19	—	3.72 (2.5)	3.47 (5.5)	4.98 (3.8)	5.03[c] (4.9)	4.96[c] (5.1)	—	4.39 (5.1; 4.1)	5.99 (8.7)	8.85	7.50[d] 6.90[d]
3	*E*(80%)	7.27 (5.3)	4.12 (6.5)	3.61 (1.4)	3.32–3.63		—	3.32–3.63		5.9[d];5.7[d];4.8[d]							
	Z(20%)	6.43 (5.6)	4.68 (8.2)	3.52	3.32–3.63		—	3.32–3.63		*f*							
4·HNO_3	β-D($^4C_1$)	3.69 (8.5)	3.27 (8.5)	3.2–3.5		3.64	—	3.2–3.5		4.84[c] (5.4)	4.89[c] (2.6)	4.49 (4.4)	—	4.60 (5.8)	5.94 (8.5)	8.80	7.50[d] 6.89[d]
4	*E*	7.37 (4.9)	4.32 (~1)	3.39	3.3–3.8		—	3.3–3.8		4.4[d];5.2[d];5.7[d]							
5·HCl	β-D($^4C_1$)[g]	3.95 (~1)	3.78 (~2)	3.0–3.7				3.0–3.7		4.85;4.90				*f*	5.45 (9.5)	9.25	7.0–7.8[f]
5	*E*	7.42 (4.9)	4.03 (8.9)	2.5–3.7		—	—	2.5–3.7		4.4[d];5.2[d];5.8[d]							
6·HNO_3	*E*	7.42 (4.5)	5.58 (3.8)	5.43 (7.4)	5.18	4.28[h] (3.1)	4.14 (5.7)	—	—	—	—	—	—	—	—	11.40	4.50[d]
7·HNO_3	*E*	7.36 (4.4)	5.49 (1.2)	5.36		5.24 (~1)	—	4.19[i] (4.7)	3.94 (7.0)	—	—	—	—	—	—	11.46	7.50[d]
8·HNO_3	*E*	7.44 (4.6)	~5.5		5.32	5.04 (3.4)	—	4.25[j] (3.4)	4.07 (6.3)	—	—	—	—	—	—	11.49	7.46[d]

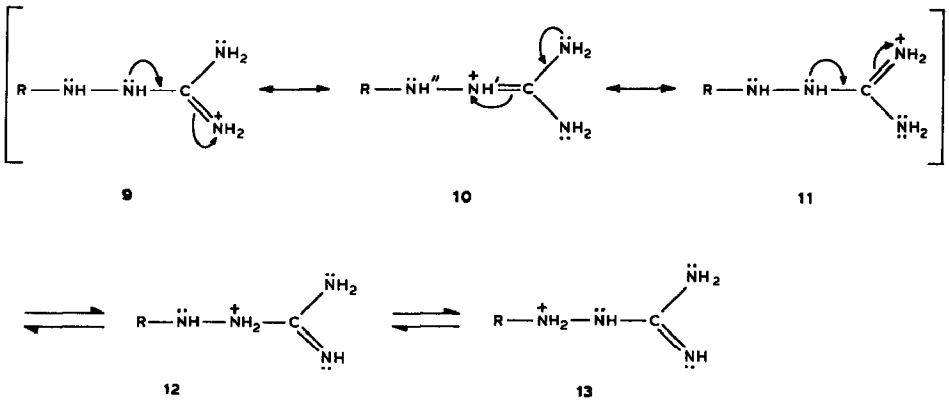
[a]In p.p.m. from Me_4Si. [b]In Hz. [c]Assignments may be interchanged. [d]Broad, partially coalesced signals. [e]5% of *Z*-isomer, H-1 at 6.57 p.p.m. ($J_{1,2}$ 4.1 Hz). [f]Overlapped by the signals of the *E*-isomer. [g]20% of the *E*-isomer present. [h]$J_{5a,5b}$ 12.5 Hz. [i]$J_{6a,6b}$ 12.7 Hz. [j]$J_{6a,6b}$ 12.3 Hz.

TABLE VI

^{13}C-N.M.R. DATA [$(CD_3)_2SO$]

Compound	*Form*	*Chemical shifts*[a]						
		C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	C_g
2·HNO_3	α-L($^4C_1$)	91.08 (152.2)	73.03	68.26;68.03		67.03	—	158.61
2	*E*	148.52 (159.5)	70.24	73.24	71.21	63.38	—	159.62
3·HNO_3	β-D($^4C_1$)	90.33 (155.0)	70.95[c]	76.90[b]	70.06[c]	77.78[b]	61.40	158.60
3	*E*	147.18 (160.8)	72.77	71.46;71.36;71.13			63.53	160.13
4·HNO_3	β-D($^4C_1$)	90.88 (152.1)	68.29	73.83	68.29	76.37	60.71	158.90
4	*E*	148.70 (161.7)		71.91;70.21;70.00;69.29			63.20	159.79
5·HNO_3	β-D($^4C_1$)	87.21 (154.4)	69.25	74.07	67.41	78.41	62.02	158.41
5	*E*	148.64 (161.4)		71.48;71.13;70.33;69.99			63.83	159.84
6·HNO_3	*E*	144.99 (171)	69.51[b]	69.26[b]	68.07	61.26	—	155.06
7·HNO_3	*E*	145.08 (171.5)	69.31	67.39	67.39	68.28	61.57	155.08
8·HNO_3	*E*	144.47 (170.5)	70.52	68.32;68.41;68.66			61.15	156.18

[a]In p.p.m. from Me_4Si. [b,c]Assignments can be interchanged pairwise.



Scheme 1. Tautomeric forms in the protonation equilibrium of glycosylaminoguanidines.

signal for H-1 and the $J_{C\text{-}1,H\text{-}1}$ value (see below) establish the β-configuration of the *manno* compound **5**. The alternative anomeric forms of **2–5** were not detected.

The ^{13}C-n.m.r. data (Table IV) corroborate these findings. The signals for C-1 were in the narrow range 89.5–90.5 p.p.m. and the $J_{C\text{-}1,H\text{-}1}$ values were close to

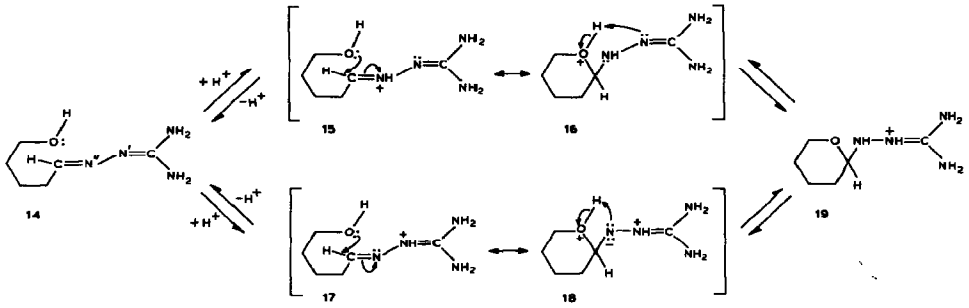
155 Hz for **2–5**. Few $J_{C\text{-}1,H\text{-}1}$ values are known for pyranosylamines but, on the basis of values published for some *N*-arylglucosylamines[49] and for pyranosyl azides[50], values of 155–158 Hz can be associated confidently with axial C-1–H-1 bonds. The $J_{C\text{-}1,H\text{-}1}$ values in Table IV therefore provide additional proof for the equatorial orientation of the C-1 substituents in **2–5** for solutions in D_2O at low pH.

The ^1H- and ^{13}C-n.m.r. data for solutions of **2**·HNO_3, **3**·HNO_3, **4**·HNO_3, and **5**·HCl in methyl sulfoxide are summarised in Tables V and VI. These data indicate the exclusive presence of the β-D-pyranoid forms for **3**·HNO_3, **4**·HNO_3, and **5**·HCl, and the α-L-pyranoid form for **2**·HNO_3, in complete accord with the situation for solutions in D_2O at low pH. The equatorial orientation of the C-1 substituent in **2–5** is favoured in both D_2O and Me_2SO at low pH. The aminoguanidine moiety is protonated under these conditions and the above observations can be rationalised in terms of the reverse anomeric effect[51,52].

Several tautomers are conceivable in the protonation equilibrium (Scheme 1). For solutions in D_2O, proton exchange is rapid on the n.m.r. time-scale and the protonated species cannot be identified. For solutions in Me_2SO, discrete signals can be observed for the NH and OH protons (Table V). The NH resonance is easily identified as a doublet, due to coupling with H-1, at 5.4–6.0 p.p.m. in the spectra of solutions of **2–5**·HX (X = NO_3, Cl) in Me_2SO (Table V). Of the remaining signals which disappear upon exchange with D_2O, a one-proton singlet at 8.8–9.2 p.p.m. and two, partially coalesced two-proton signals at ~6.9 and ~7.5 p.p.m. can be assigned to *N*-bonded protons. Such a distribution of the NH signals is compatible only with the preponderance of the tautomers **9–11** in the protonation equilibrium. Also, this tautomeric form should be the most favoured because of mesomerism, as opposed to **12** or **13** where the possibility for mesomerism is much more restricted. Furthermore, the difference in chemical shifts of the two NH signals indicates that the charge distribution within **9–11** should be close to that depicted in **10**. These conclusions were confirmed by the ^{15}N-n.m.r. data for **3**·HNO_3. In the ^1H-coupled ^{15}N-n.m.r. spectrum, there are two doublets at 109.7 ($^1J_{N,H}$ 102.1 Hz) and at 87.8 p.p.m. ($^1J_{N,H}$ 81.0 Hz). In view of the effect of hybridisation on $^1J_{N,H}$ values[53], the increased value of one of the couplings with respect to the other is a strong indication of an increased positive charge on the pertinent N. This finding is compatible only with a tautomer having a charge distribution close to that in **10**. The triplets expected for the terminal NH_2 groups are not clearly seen in the ^1H-coupled ^{15}N-n.m.r. spectrum of **3**·HNO_3 because proton exchange, at a rate comparable to $(^1J_{N,H})^{-1}$, results in broad, partially averaged signals; application of broad-band proton decoupling allowed the observation of still very broad ($\Delta\nu_{1/2}$ ~40 Hz) but discernible signals at ~81 and ~75 p.p.m.

Compounds **6–8**·HNO_3 were synthesised in order to obtain n.m.r. parameters characteristic for the acyclic hydrazone form. The chemical shifts of the signals for H-1 of these derivatives in solution in D_2O and Me_2SO (Table III and V, respectively) are in reasonable agreement with values expected for the *E*-hydrazone structure (see above); *Z*-isomers could not be detected. The chemical

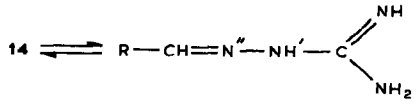
shifts of the signals for H-1 of **2–5** observed in solutions in D_2O at high pH (Table III) are close to those found for **6–8**·HNO_3, so that **2–5** exist mainly in the *E*-forms under these conditions; ~2% of the *Z*-isomers of **2** and **4** could be detected. The chemical shifts of the signals of C-1 for **2–5** in solutions in D_2O at high pH (Table IV) were also in the range (150–155 p.p.m.) expected[6,35,37] for the acyclic hydrazone structure. The $J_{C\text{-}1,H\text{-}1}$ values were in the range 159–164 Hz (Table IV) and also



Scheme 2. Mechanism of the ring–chain interconversion between glycosylaminoguanidine and carboximidamidehydrazone forms.

indicate the *E*-configuration in view of the values found for L-arabinose *E*-oxime[44] (163.2 Hz) and for some aldose *E*-phenylhydrazones[6] (~165 Hz). The chemical shifts of the signals for C-1 in the acetylated derivatives **6–8**·HNO_3 were ~10 p.p.m. smaller, and the $J_{C\text{-}1,H\text{-}1}$ values were ~10 Hz larger, than those measured in the respective non-acetylated carboximidamidehydrazones **2–4**. These differences may reflect different states of ionisation of the carboximidamidehydrazone moiety which, in the former, is in an *N*-protonated form, whereas it is non-protonated in the latter in solution in D_2O at high pH.

It is clear from the evidence presented above that aldose carboximidamidehydrazones exist in aqueous solution as an equilibrium mixture of the pyranosylaminoguanidine forms with the C-1 substituent equatorial (**19**) and the *E*-acyclic forms (**14**), as shown in Scheme 2. The equilibrium concentrations of **14** and **19** are dependent on the pH, and a possible mechanism is shown in Scheme 2. There is no evidence at present concerning the site of the first proton attack, but N″ (**14**) seems



20

the most probable (→**15**→**16**→**19**), since initial protonation at N′ (→**17**→**18**→**19**) would involve a structure with two-coordinated negatively charged nitrogen (**18**). A similar mechanism may operate in the pH-dependent ring-chain tautomerism of

aldose hydrazones[35], oximes[44], and related derivatives. An intramolecular solvent-mediated, protonation–deprotonation mechanism has been proposed[4] for the ring-chain tautomerism observed for some aldose acylhydrazones.

In solution in Me_2SO, **2–5** existed mainly in the acyclic form **14**, and minor amounts of the *Z*-isomers could be detected for **2** and **3**. In addition to geometric isomerism about the C=N bond, tautomerism in the guanidino moiety (**14** ⇌ **20**) must also be considered. However, ^{15}N chemical shifts determined for **2** supported the preponderance of tautomer **14**. The broad-band ^1H-decoupled ^{15}N-n.m.r. spectrum of **2** in solution in Me_2SO displayed resonances at 67.9, 69.7, 228.6, and 354.7 p.p.m. By comparison with the ^{15}N chemical shifts for hydrazones[54,55] and oximes[54], the signal at 354.7 p.p.m. is assigned to the azomethine nitrogen, N″. Similarly, the first two resonances must arise from sp^3-hybridised amino nitrogens[56,57]. On the other hand, a chemical shift of 228.6 p.p.m. indicates[56,57] the presence of another sp^2-hybridised imino nitrogen, *e.g.*, N′ in **14**. Such an sp^3-nitrogen as N′ in **20** would be expected[56,58] to resonate at much higher field (140–170 p.p.m.). A minor contribution of tautomer **20** cannot be excluded completely on the basis of ^{15}N chemical shifts alone.

EXPERIMENTAL

General. — Melting points were determined on a Boetius heating-stage microscope Optical rotations were measured with a model Schmidt–Haensch polarimeter. T.l.c. was performed on Kieselgel GF_{254} (Merck), using 1-butanol–acetic acid–water (4:1:1) for **2–5**·HX (X = Cl, NO_3) and methanol–ethyl acetate (1:1) for **6–8**·HX (X = Cl, NO_3).

The aminoguanidine·HNO_3·H_2O and aminoguanidine·HCO_3 were commercial products. Aminoguanidine·HCl, prepared by treatment with dilute hydrochloric acid and recrystallised from water–ethanol, had m.p. 163–165° (ref. 59). 2,3,4,5-Tetra-*O*-acetyl-*aldehydo*-L-arabinose[60], 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-glucose[61], and 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose[62] were synthesised by the reported procedures.

200-MHz ^1H-, 50.3-MHz ^{13}C-, and 40.6-MHz ^{15}N-n.m.r. spectra were recorded on Bruker WP 200 SY and AM 400 spectrometers. External nitromethane was used as the primary reference for the ^{15}N chemical shifts which, in turn, were converted[58] into the external ammonia reference scale. Typical acquisition parameters for the broad-band ^1H-decoupled ^{15}N-n.m.r. spectra were: pulse angle, 25°; relaxation delay, 5 s; acquisition time, 0.25 s. The ^1H-coupled ^{15}N-n.m.r. spectrum was obtained by the DEPT polarisation transfer method[63] optimised for $^1J_{N,H}$ 90 Hz. The pH of the solutions of **2–5** in D_2O was adjusted with either 30% NaOD or 20% DCl solutions in D_2O. Otherwise, the free carboximidamide-hydrazones or their salts were dissolved in the specified solvents and the spectra were measured without any adjustment of the pH. For the study of the pH-dependence shown in Fig. 1, **4** (80 mg) was dissolved in glycine buffer (10 mL; 0.750 g of

glycine and 0.585 g of NaCl dissolved in D_2O to 100 mL), and the pH was adjusted with 0.1M NaOD in D_2O. The exact pH-value of this stock solution was determined using a pH meter, the ^{1}H-n.m.r. spectrum was obtained on a 0.5-mL aliquot, and then the pH of the stock solution was adjusted to the next pH value.

Condensation of aldoses with aminoguanidine salts. — To a solution of the appropriate aldose (10 mmol, see Table I) in water (1.6 mL) was added the aminoguanidine salt (10 mmol, Table I), and the solution kept at 100° for 25 min. The condensation product was precipitated by the addition of dry ethanol (15–22 mL) and filtered off, and the crude product was recrystallised from the solvents given in Table I. The physical constants and analytical data are listed in Table I.

Preparation of the free bases **2–5**. — The **2–5**·HX (10 mmol, X = Cl, NO_3, Table I) were dissolved in water (4–6 mL) and eluted from a column (2.5 × 22 cm) of Dowex 2-X4 (HO^-) resin with water. The eluates (180–200 mL) were concentrated to dryness under reduced pressure and the residues were recrystallised from the solvents in Table I.

Acetylated aldose carboximidamidehydrazones. — To a solution of the acetylated *aldehydo*-aldose (10 mmol) in water (16 mL, warming) was added **1**·HX (10 mmol, X = Cl, NO_3) after cooling. The precipitates were collected after 5 h, washed with water, and recrystallised as indicated in Table II. The physical constants and analytical data are listed in Table II.

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