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Potentiometric and spectroscopic studies of the binding of copper(II) ions by aminodeoxy derivatives of 1,6-anhydro-β-D-glucopyranose*

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ABSTRACT

Potentiomentric and spectroscopic studies of the complexes of Cu^{2+} with amino-1,6-anhydrodeoxy sugars indicated that the amino nitrogen acts as an anchoring donor. The conformation of the sugar ring, the 1,6-anhydro ring, and the position of the amino and hydroxyl groups are critical for the stability of the complex.

INTRODUCTION

2-Amino-2-deoxy-D-glucose (GlcN), 2-amino-2-deoxy-D-galactose (GalN), and 2-amino-2-deoxy-D-mannose (ManN) act[1-5] as bidentate ligands towards Cu^{2+}, Ni^{2+}, and Co^{2+} with the amino group as a major donor and a deprotonated hydroxyl group as the second donor. The results for aminodeoxy sugars and their methyl glycopyranosides[5] indicated that various hydroxyl groups can be involved in the binding of metal ions and that the relative position of the hydroxyl group may have a critical influence not only on the structure but also on the stability of the species formed. The above aminodeoxy sugars are effective chelating agents for Cu^{2+}, and the position of the hydroxyl group involved may vary the stability constant of the complex by 2–3 orders of magnitude[5].

In comparison with the aminodeoxyhexoses, their 1,6-anhydro derivatives have limited flexibility[6]. On the basis of physicochemical measurements[6,12], it was proposed that the major conformation of 1,6-anhydro sugars is $^1C_4$, whereas that of the parent aminodeoxy sugar is usually $^4C_1$. Hence, a study of the co-ordination of amino-1,6-anhydrodeoxy sugars with Cu^{2+} may give more precise information about the relation

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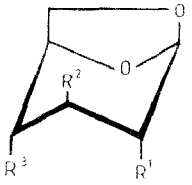
between the conformation of the ligand and its binding ability. We now report potentiometric and spectroscopic studies of the complexes of the 2-amino-2-deoxy (**1**), 2-deoxy-2-methylamino (**2**), 3-amino-3-deoxy (**3**), and 4-amino-4-deoxy (**4**) derivatives of 1,6-anhydro-β-D-glucopyranose with Cu^{2+}.



1 $R^1=NH_2, R^2=R^3=OH$
2 $R^1=NHCH_3, R^2=R^3=OH$
3 $R^1=R^3=OH, R^2=NH_2$
4 $R^1=R^2=OH, R^3=NH_2$

EXPERIMENTAL

2-Amino-1,6-anhydro-2-deoxy-β-D-glucopyranose[7] (**1**, AGlcN), the *N*-methyl derivative[8,9] (**2**, AGlcMeN), 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose[10] (**3**, AGlc3N), and 4-amino-1,6-anhydro-4-deoxy-β-D-glucopyranose[11] (**4**, AGlc4N) were obtained as described.

Potentiometric studies. — The stability constants of the H^+ and Cu^{2+} complexes were calculated from the pH titration data obtained at 25° with a Radiometer PHM64 pH meter, using total volumes of 3 mL. A calibrated Hamilton microsyringe was used. Changes in pH were followed by using a glass–calomel electrode calibrated for H^+ activity. The relation between activity and concentration was calculated daily by titration[13] with HNO_3. All solutions were prepared with 0.15M KNO_3, 2.5×10^{-3}M ligand, and 1:2, 1:4, and 1:6 ratios of metal to ligand. Stability constants were calculated with the aid of the SUPERQUAD program[14], which allows for the simultaneous refinement of the stability constants together with total concentrations of ligand and hydrogen. The standard deviations reported refer to random errors only. These calculations, however, gave a good indication of the importance of the particular species in the equilibrium.

Spectroscopic measurements. — Absorption spectra were recorded with a UVIKON 810 P spectrophotometer. E.p.r. measurements were carried out with a Varian E-9 spectrometer operating at 9.3 GHz and −171°. C.d. spectra were obtained with a Jobin–Yvon Mark III spectropolarimeter. The concentration of Cu^{2+} was adjusted to 3×10^{-3}M and the ratio of the metal to the ligand was fixed at 1:4.

RESULTS AND DISCUSSION

Protonation constants (log β values) for the ligand studied are given in Table I. Potentiometric titration clearly demonstrated one protonation step at pH ~7, which corresponded to the nitrogen donor of the ligands. The protonation constant of AGlcN (**1**) is lower by 0.6 log unit than that of GlcN, which indicates an electron-withdrawing effect of the O-5–C-1–O-1 group in the 1,6-anhydro derivatives. The nitrogen in the *N*-methyl derivative **2** (AGlcMeN, Table I) is slightly more basic than that in **1**. The variation of the position of the amino group to C-3 (**3**, AGlc3N) or C-4 (**4**, AGlc4N) also increased the pK values due to the larger distance from the 1,6-anhydro ring. The data in Table I indicate that each 1,6-anhydro derivative is slightly less basic than the parent aminodeoxy sugar.

The formation constants for the Cu^{2+} complexes are also given in Table I and the spectroscopic data in Table II. AGlcN (**1**) and AGlcMeN (**2**) form three complexes (Fig. 1). According to the e.p.r. data, the first complex formed is an oligonuclear (dinuclear) form with coupled metal ions. The potentiometric data can be fitted easily to the dimer model (e.p.r. silent) that contains the Cu_2L_4 complex and the two monomeric species CuL_2H_{-1} and CuL_2H_{-2}. In the pH range 5–7, in which no e.p.r. spectra could be observed, the dinuclear species formed is seen in both the absorption and c.d. spectra (Table II). The presence of c.d. spectra indicates that Cu^{2+} is bound directly to the optically active ligand. In the dinuclear species, the major binding site, as in the parent aminodeoxy sugar complexes[1–5], is the amino nitrogen. This co-ordination is reflected by the c.d. spectra, which exhibit a band at 300 nm that can be assigned[1] as the $NH_2 \rightarrow$ Cu(II) charge-transfer transition. The lack of the e.p.r. spectra corresponds precisely to the pH range in which potentiometric data indicate the formation of the dinuclear species.

TABLE I

Stability constants (log β) for Cu^{2+} complexes of the 1,6-anhydro-β-D-glucopyranose derivatives and D-GlcN[16], D-GalN[3], and D-ManN[5a]

Species[b]	*AGlcN* (**1**)	*AGlcMeN* (**2**)	*AGlc3N* (**3**)	*AGlc4N* (**4**)	*GlcN*	*GalN*	*ManN*
LH	7.07(1)[c]	7.30(1)	7.32(1)	7.48(1)	7.70	7.84	7.59
CuL						4.20	
CuL_2			6.86(1)		9.02	9.13	9.68
Cu_2L_4	18.63(5)	17.92(5)		20.03(4)			
CuL_2H_{-1}	0.71(2)	0.28(2)	−0.36(1)	1.49(2)		2.37	2.72
CuL_2H_{-2}	−8.05(4)	−8.05(3)	−8.20(1)	−6.89(3)	−5.26	−5.21	−3.66
CuL_2H_{-3}				−17.25(4)	−13.77	−15.44	−13.00
pK'[d]	8.76	8.33	7.84	8.38		7.58	6.38

[a] At 25° and I = 0.15M KNO_3. [b] LH ligand protonated at amino nitrogen; LH_{-n} corresponds to ligand with "n" hydroxyl groups deprotonated and bound to Cu^{2+}. [c] Standard deviations are given in parentheses. [d] log $K' = \log \beta_{12\text{-}1} - \log \beta_{12\text{-}2}$.

TABLE II

Spectroscopic data for the Cu^{2+} complexes of the 1,6-anhydro sugar derivatives

Species	*E.p.r.*		*Absorption*		*C.d.*		
	A [G]	$g_\parallel$	λ[nm]	(ε)	λ[nm]^a	($\Delta\varepsilon$)	
AGlcN (**1**)							
Cu_2L_2	No spectrum		678	(37)	740	(−0.13)	B
					b595	(+0.08)	E
					sh320	(+1.20)	$NH_2 \rightarrow Cu$
					251	(−3.30)	intraligand
CuL_2H_{-1}	150	2.27	615	(62)	671	(+0.52)	B
					608	(−0.18)	E (I_a)
					544	(+0.33)	E (I_b)
					375	(−0.93)	
					320	(+2.00)	$NH_2 \rightarrow Cu$
					280	(−2.50)	$O^- \rightarrow Cu$
					250	(−3.61)	intraligand
CuL_2H_{-2}	150	2.27	613	(72)	740	(+0.60)	B
					sh620	(+0.20)	E (I_a)
					580	(+0.52)	E (I_b)
					314	(+6.20)	$NH^- \rightarrow Cu$
					270	(−10.11)	$O^- \rightarrow Cu$
AGlcMeN (**2**)							
Cu_2L_2	No spectrum		690	(30)	730	(−0.05)	B
					sh630	(+0.02)	E (I_a)
					b578	(+0.03)	E (I_b)
					298	(+1.53)	$NH_2 \rightarrow Cu$
					260	(−2.30)	intraligand
CuL_2H_{-1}	135	2.28	640	(67)	688	(+0.18)	B
					597	(−0.17)	E (I_a)
					sh558	(−0.06)	E (I_b)
					382	(−0.27)	
					320	(+0.72)	$NH_2 \rightarrow Cu$
					264	(−2.55)	$O^- \rightarrow Cu$
CuL_2H_{-2}	135	2.28	630	(75)	732	(−0.12)	B
					sh668	(+0.09)	E (I_a)
					548	(+0.08)	E (I_b)
					306	(+0.64)	$NH^- \rightarrow Cu$
					274	(−2.70)	$O^- \rightarrow Cu$

Species	*E.p.r.*		*Absorption*		*[a]C.d.*		
	$A_{\parallel}$[G]	$g_{\parallel}$	λ[nm]	(ε)	λ[nm][a]	($\Delta\varepsilon$)	
AGlc3N (**3**)							
CuL_2	133	2.35	710	(36)	756	(+0.01)	A
					658	(−0.01)	B + E
					290	(+0.23)	O^-,NH_2→Cu
					248	(−0.09)	intraligand
CuL_2H_{-1}	182	2.25	690	(47)	760	(+0.01)	A
					602	(−0.03)	B + E
					284	(+0.50)	O^-,NH_2→Cu
					244	(−0.39)	intraligand
CuL_2H_{-2}	182	2.25	640	(49)	696	(+0.02)	A
					574	(−0.50)	B + E
					278	(+0.79)	O^-,NH_2→Cu
					240	(−0.59)	intraligand
AGlc4N (**4**)							
Cu_2L_4	No spectrum		60	(42)	732	(+0.05)	B
					619	(+0.02)	E (Γ_a)
					500	(+0.01)	E (Γ_b)
					300	(−2.41)	NH_2→Cu
					252	(+3.08)	intraligand
CuL_2H_{-1}	150	2.27	605	(65)	680	(−0.14)	B
					605	(+0.14)	E (Γ_a)
					534	(−0.05)	E (Γ_b)
					372	(+0.25)	[b]
					324	(−0.38)	NH_2→Cu
					278	(+0.91)	O^-→Cu
					261	(+1.10)	intraligand
CuL_2H_{-2}	150	2.27	624	(77)	740	(+0.17)	B
					652	(−0.08)	E (Γ_a)
					562	(−0.14)	E (Γ_b)
					322	(−0.62)	NH_2→Cu
					274	(+1.80)	O^-→Cu
CuL_2H_{-3}	150	2.27	636	(81)	740	(+0.30)	B
					594	(−0.26)	E (Γ_a)
					sh550	(−0.18)	E (Γ_b)
					320	(−0.08)	NH_2→Cu
					275	(+2.16)	O^-→Cu

[a] sh, Shoulder; b, broad. [b] This band cannot be assigned precisely.

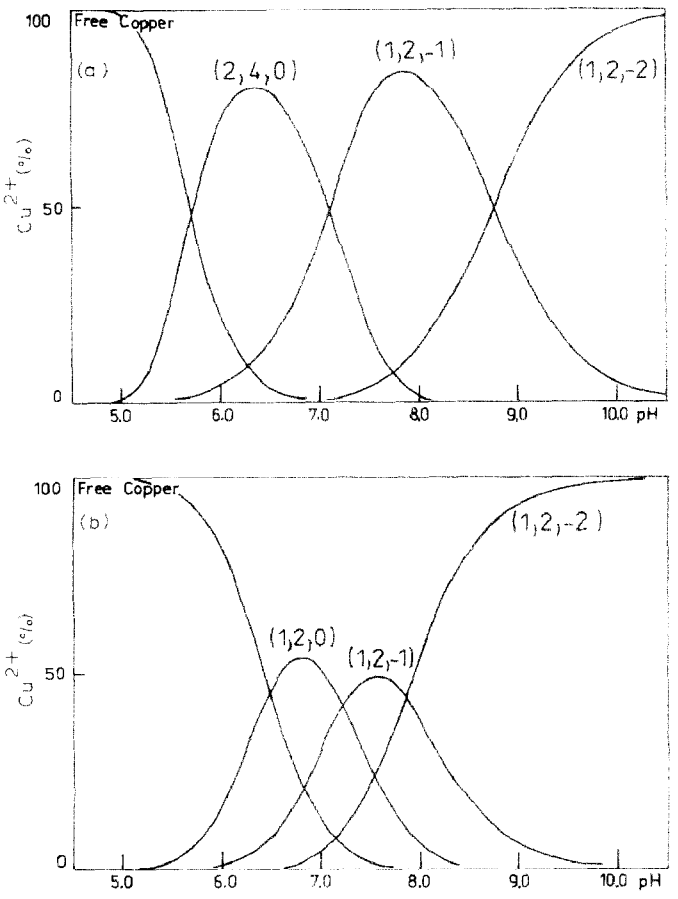


Fig. 1. Concentrations of the complexes of Cu^{2+} with (*a*) AGlcN (**1**) and AGlc3N (**3**); metal-to-ligand molar ratio 1:4 and C_M = 0.001M; (2,4,0) = CuL_2, (1,2,0) = CuL_2, (1,2,-1) = CuL_2H_{-1} and (1,2,-2) = CuL_2H_{-2}

The involvement of the amino and deprotonated hydroxyl groups in the formation of CuL_2H_{-1} and CuL_2H_{-2} is also indicated clearly by the c.d. spectra (Table II) in which the $O^- \rightarrow Cu(II)$ and $NH_2 \rightarrow Cu(II)$ charge-transfer transitions[1,15] are observed at ~280 and ~320 nm, respectively. The complete assignments of the spectroscopic data are given in Table II.

The pattern of co-ordination for AGlcN (**1**) and AGlcMeN (**2**) is similar to that for AGlc4N (**4**), but the complexes for **4**, including the dinuclear species, are distinctly more stable (Table I). At pH > 10, the major species appears to be the CuL_2H_{-3} complex which was not observed for **1**–**3**. However, deprotonation of the CuL_2H_{-3} complex was observed[1,2,5,16] for GlcN, GalN, and ManN (Table I). The formation of the CuL_2H_{-3} species may be due[5] to deprotonation and binding of the second hydroxyl group which is in a favourable position for binding to Cu^{2+}. The CuL_2H_{-3} complex for AGlc4N (**4**) is the least stable species when compared to the complexes with aminodeoxy sugar

ligands. Molecular models indicate that, for AGlc4N (**4**), the co-ordination of two deprotonated hydroxyl donors simultaneously with the amino nitrogen is unlikely for monomeric complexes.

At lower pH for AGlc3N (**3**), the e.p.r. and potentiometric data indicate the formation of the monomeric CuL_2 species as found for the parent aminodeoxy sugars (Tables I and II, Fig. 1b). The species formed is considerably less stable than the corresponding complexes of GlcN or other aminodeoxy sugars (Table I) due to the less favourable position of hydroxyl groups. The hydroxyl groups, when protonated, may interact with Cu^{2+} co-ordinated to the amino nitrogen to stabilise the CuL or CuL_2 complexes[1,5]. Also, the other two complexes found, namely CuL_2H_{-1} and CuL_2H_{-2}, are the least stable species in Table I. Thus, the positions of hydroxyl groups make AGlc3N (**3**) the least favourable for the formation of complexes.

The results in Tables I and II show that the formation of the dinuclear species is limited to three 1,6-anhydro derivatives in which the nitrogen donor is vicinal to the 1,3-dioxolane ring and suggest that this ring may play a key role in the formation of dinuclear species from two monomeric CuL_2 units. The vicinity of two Cu^{2+} ions may broaden considerably the e.p.r. spectra due to strong dipole–dipole interactions. The conformation of the ligand can also affect the formation of dinuclear species. The ligands **1**, **2**, and **4** favour the $^1C_4$ conformation in which the Cu^{2+} bound to nitrogen is close to O-5 and may allow interaction. For AGlc3N (**3**), there is an equilibrium between chair ($^1C_4$) and boat ($B_{0,3}$) forms[6,12]. Protonation of the amino group (low pH) favours the boat conformation. Moreover, only in the boat conformation can Cu^{2+} interact simultaneously with the nitrogen and hydroxyl groups of the ligand. However, in this situation, the Cu^{2+} bound to amino nitrogen is remote from the 1,3-dioxolane ring and any interaction with or *via* these oxygens is unlikely.

The chair conformation of AGlcN (**1**), AGlcMeN (**2**), and AGlc4N (**4**) forces the formation of 6-membered chelate rings in CuL_2H_{-1} and CuL_2H_{-2} complexes, such that only O-4 can be co-ordinated simultaneously with N-2 or O-2 with N-4. This explains why the stabilities of the complexes of the 1,6-anhydro sugar derivatives are lower than those of the parent aminodeoxy sugars. This suggestion is supported by the values of log $K' = \log \beta_{CuL_2H_{-1}} - \log \beta_{CuL_2H_{-2}}$, which characterise the metal-induced proton dissociation from the hydroxyl group that forms the chelate ring. The values obtained for the 1,6-anhydro sugar derivatives are one or more units lower than those obtained for GlcN, GalN, or ManN (Table I). It is also likely that the 1,3-dioxolane ring may affect the stability of the complexes by imposing the $^1C_4$ conformations.

The spectroscopic data in Table II suggest that most of the complexes may have lower than tetragonal symmetry, as indicated by the relatively low $A_{\parallel}$ values[17] and the splitting of the *d–d* transitions into A, B, and E bands[18] induced by the bulky and rigid ligands.

Thus, amino-1,6-anhydrodeoxy sugars are relatively effective ligands for Cu^{2+}, although less effective than the parent aminodeoxy sugars. The amino nitrogen is the major site of binding at pH 5.5. The stability constants (Table I and refs. 1–5) clearly indicate that, although the amino nitrogen is the most effective in binding Cu^{2+}, the

position of the hydroxyl groups may affect the stability by up to above four orders of magnitude.

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