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STABILITY AND STRUCTURE OF COPPER(II) COMPLEXES WITH 2-AMINO-2-DEOXY-D-MANNOSE AND SOME DERIVATIVES THEREOF

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ABSTRACT

Potentiometric and spectroscopic studies indicate that 2-amino-2-deoxy-D-mannose (ManN), its methyl α-glycopyranoside, and methyl 2-amino-2-deoxy-α,β-D-galactopyranoside are good chelating agents for cupric ions. The stability constants for the complexes with the *manno* compounds are higher than those of 2-amino-2-deoxy-D-galactose (GalN) and 2-amino-2-deoxy-D-glucose (GlcN). The primary binding site is the amino group and the most effective secondary site in the *manno* compounds is HO-3. Comparison of the co-ordination abilities of GalN, GlcN, ManN, and their methyl glycopyranosides indicates that various hydroxyl groups can be involved in the binding of metal ions. The stability constants of the Ni(II) and Co(II) complexes with ManN are also presented.

INTRODUCTION

Amino sugars can form strong complexes with transition metal ions and hence can be important chelating agents[1–9]. 2-Amino-2-deoxy-D-glucose (GlcN) and 2-amino-2-deoxy-D-galactose (GalN) act as bidentate ligands with the amino group as the major donor towards such metal ions as Cu(II), Ni(II), and Co(II), and with one of the hydroxyl groups as the second donor. For GalN or GlcN, the

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second donor appears[1,2,6,9] to be HO-1, but the results obtained for the complexes of methyl 2-amino-2-deoxy-β-D-glucopyranoside (β-GlcN-OMe) indicate that other hydroxyl groups may also be involved in the metal ion binding[5]. In 2-amino-2-deoxy-D-mannose (ManN), HO-1 and HO-3 could be considered as sterically favourable as second donors. In order to obtain a more precise description of the binding ability of amino sugars, the copper(II) complexes of ManN, its methyl α-glycoside (α-Man-OMe), and αβ-GalN-OMe have been studied.

EXPERIMENTAL

Materials. — Methyl 2-amino-2-deoxy-β-D-glucopyranoside hydrochloride {m.p. 188–189°, $[\alpha]_D^{25}$ −27° (*c* 1, water); *cf.* ref. 11} was prepared from 2-amino-2-deoxy-α-D-glucose hydrochloride by the method of Viscontini and Meier[10]. Treatment of 2-amino-2-deoxy-α-D-mannose with dry HCl in refluxing methanol for 12 h and recrystallisation of the product from ethanol–light petroleum gave methyl 2-amino-2-deoxy-α-D-mannopyranoside hydrochloride, m.p. 168–170° (dec.), $[\alpha]_D^{25}$ +120° (*c* 1, water, after the addition of 1 equiv. of base; *cf.* ref. 12). Similar treatment of 2-amino-2-deoxy-α-D-galactose hydrochloride gave a 77:23 αβ-mixture of methyl 2-amino-2-deoxy-D-galactopyranoside hydrochloride as indicated by the ^{1}H-n.m.r. data (D_2O): α anomer, δ 4.82 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 3.21 (s, 3 H, MeO-1); β anomer, δ 4.35 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.36 (s, 3 H, MeO-1); *cf.* ref. 13 for the α anomer.

Potentiometric measurements. — Stability constants of proton and metal ion complexes were calculated from the pH titration data collected at 25° with a Radiometer PHM84 pH-meter, using total volumes of 3 mL. A Tacussel micrometer syringe was used, which was calibrated by both weight titration and the titration of standardised materials. Changes in pH were followed with a combined glass electrode calibrated for H^+ activity. The relationship between activity and concentration was calculated daily by titration[14] with HNO_3. All solutions were 0.15M (KNO_3) and ~1.5mM (amino sugar). The metal-to-ligand ratios were ~1:4, ~1:10, and ~1:11 for copper(II), nickel(II), and cobalt(II), respectively. High ligand-to-molar ratios were necessary in order to study the nickel and cobalt complexes because of their low stabilities. Hence, the accuracy of the results is significantly lower than for those of the copper complexes. Stability constants were calculated with the SUPERQUAD computer program[15] modified for an IBM PC and compatibles equipped with an 8087 coprocessor. The program allowed the simultaneous refinement of stability constants together with the total concentrations of ligands and protons.

Instruments. — Absorption spectra were recorded on a Beckman Acta Model VII spectrophotometer with metal ion concentrations of 5mM. E.s.r. spectra of copper(II) complexes were recorded on a Varian E-9 spectrometer (X-band) at 110 K. ^{1}H-N.m.r. spectra (200 MHz) were recorded with a Bruker AC-200 spectrometer. Optical rotations were determined with a Perkin–Elmer 241 polarimeter.

RESULTS AND DISCUSSION

*Copper(II)–2-amino-2-deoxy-*D*-mannose complexes.* — The protonation constant for ManN is close to those for GlcN and GalN (Table I) and corresponds to the dissociation of an amino group. As a result, the binding abilities of the amino group in the amino sugars were similar. The formation of the (110) and (120) complexes (the numbers refer to the metal ion, the ligand, and ionised hydroxyl groups, respectively; see Table I) also supports this assumption. In each of these complexes, the cupric ion binds to the amino nitrogen. The (120) species formed by GalN and GlcN have similar stability (Table I) and are slightly less stable than those formed by ManN. This finding suggests that, although the nitrogen of the amino sugar ligand is a main binding site of the Cu(II) ion, the involvement of a neighbouring protonated hydroxyl group in the co-ordination is likely. Strong support for this assumption was provided by a study of the methyl glycosides of GalN and GlcN. Both $\alpha\beta$-GalN-OMe and β-GlcN-OMe, in which HO-1 is blocked, form (110) and (120) complexes that are considerably weaker than those of the parent amino sugars (Table I). Deprotonation of the (120) complex gives a (12-1) species in which one of the co-ordinated ligands has an ionised hydroxyl group and is chelated via NH_2 and O^-. Further proton dissociation results in the formation of two such chelate rings and a stable (12-2) complex in basic solutions (Fig. 1). The (12-1) species becomes the preponderant complex when HO-1 is blocked ($\alpha\beta$-GalN-OMe and β-GlcN-OMe; Fig. 2 and ref. 5). The high concentration of the (12-1) complex results mainly from the low stability of the (120) complexes, especially those of β-GlcN-OMe (Table I). The formation of (12-1) complexes was observed with GalN[9] and ManN (Table I, Fig. 1). The proportion of the (12-1) complex formed by GlcN was too small to be identified from the potentiometric data. The results reported in Table I show that the most effective chelates are formed by ManN, and the (12-2) complex of ManN is more stable by ~1.5 orders of magnitude than those of GalN and GlcN. The similar stabilities of the (12-2) complexes of GalN and GlcN indicate that the same hydroxyl group is involved in the binding of the metal ion, *i.e.*, HO-1[1,2,5,6,9]. The major differences in the stability of complexes of ManN and those of GalN and GlcN indicate that the hydroxyl group of ManN involved in the co-ordination is not HO-1. Comparison of the structures of the three amino sugars suggests that HO-3 is the second donor of ManN. Since the free sugars are $\alpha\beta$-mixtures and only β-ManN, a minor component of the equilibrium, can co-ordinate through O-1, complexing at O-3 becomes important. The position of HO-3 in ManN is sterically more favourable than in GalN and GlcN. The resulting (NH_2,O-3$^-$) chelate ring is 5-membered, as is that formed by amino NH_2 and O-1$^-$. E.s.r. data support the potentiometric findings, as shown by the parameters and assignments in Table II.

The stabilities of the Ni(II) and Co(II) complexes with ManN, GlcN, and GalN are similar, but they are considerably lower than those of the Cu(II) complexes (Table I). The stability of the (12-2) species with ManN is slightly higher

TABLE I

STABILITY CONSTANTS (log β)[a]

	pqr	*ManN*[b]	*α-ManN-OMe*[b]	*GlcN*[c]	*β-GlcN-OMe*[d]	*GalN*[e]	*αβ-GalN-OMe*[b]
Cu	011	7.59 (0.005)	7.47 (0.01)	7.70	7.69	7.84	7.75 (0.005)
	110		4.81 (0.03)	5.12[f]	4.13	(4.20)[g] 5.23[f]	4.40 (0.05)
	120	9.68 (0.03)		9.02 8.85[f]	7.52	9.13 9.02[f]	8.40 (0.14)
	12-1	2.72 (0.08)	2.91 (0.02)		1.38	2.37	2.27 (0.02)
	12-2	−3.66 (0.04)	−4.29 (0.05)	−5.26	−6.85	5.21	−5.18 (0.04)
	12-3	−13.0 (1)	−13.4 (1)	−13.77		−15.44	
	12-4		−23.7 (1)				
Ni	110	—		—	3.10	—	
	120	6.11 (0.05)		6.43	—	5.96	
	12-1	−2.49 (0.09)		−3.03	−2.59	−3.08	
	12-2	−11.08 (0.07)		−12.13	−12.13	−12.45	
Co	110	—		—	2.93	—	
	120	—		4.09	—	6.50	
	12-1	—		−3.89	−1.94	—	
	12-2	−11.66 (0.08)		−13.08	−10.75	−12.01	

[a] $\beta = [M_pL_qH_r]/[M]^p[L]^q[H]^r$, where M is the metal ion, L is the ligand, and H is an ionised OH group. Standard deviation in parentheses. [b] This work. [c] Refs. 1 and 2. [d] Ref. 5. [e] Ref. 9. [f] Stability constants obtained from polarographic measurements (ref. 6). [g] Less reliable stability constants, due to the low concentration of the complex.

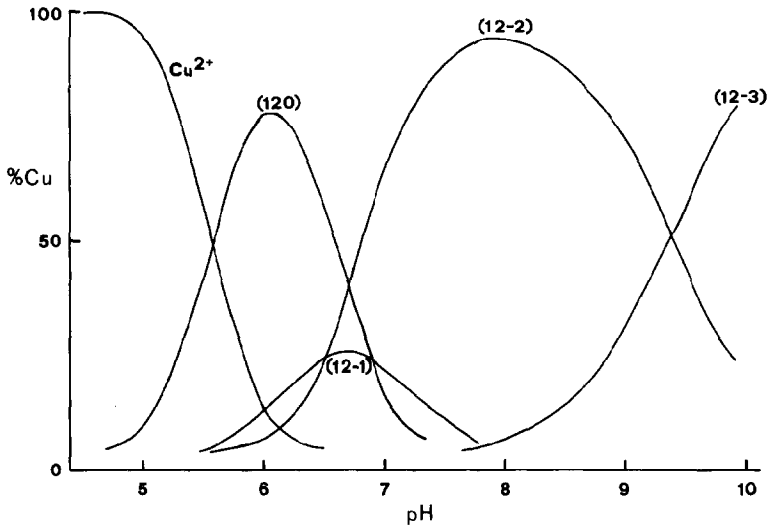

Fig. 1. Species distribution in the copper(II)–ManN system (4:1 ligand-to-metal ratio).

than those for GalN and GlcN, and this difference could also be a result of the involvement of different hydroxyl groups in the metal ion co-ordination.

*Copper(II)–methyl 2-amino-2-deoxy-α-*D*-mannopyranoside (α-ManN-OMe) system.* — Evaluation of the potentiometric data indicates the presence of five complex species in this system (Table I, Fig. 3). The first complex formed, (110), is a major species at pH ~5.9 and its stability is higher than that of the corresponding complexes of the other methyl glycosides (Table I), but slightly lower than that of the corresponding complex with GlcN or GalN. This finding suggests the amino nitrogen as the main binding site, with some stabilising effect resulting from

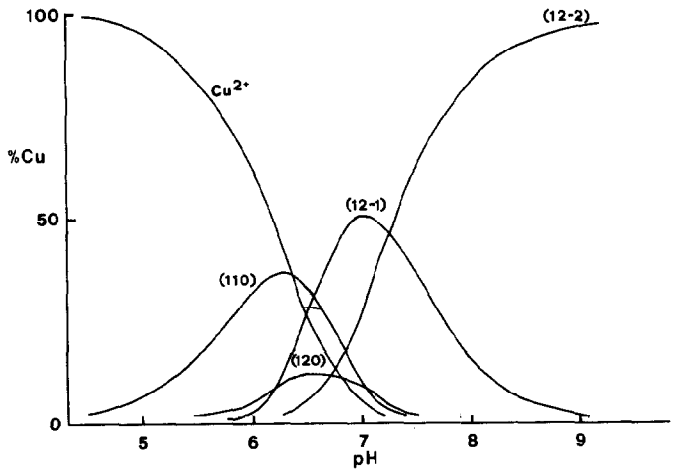

Fig. 2. Species distribution in the copper(II)–αβ-GalN-OMe system (4:1 ligand-to-metal ratio).

TABLE II

E.S.R. DATA ($g_{\|}$ AND $A_{\|}$ VALUES) FOR THE COPPER(II) COMPLEXES [a]

pqr[b]	*ManN*[c]	*α-ManN-OMe*[c]	*GlcN*[d]	*β-GlcN-OMe*[e]	*GalN*[f]	*αβ-GalN-OMe*[c]
110	2.331 (152)	2.334 (146)		2.341 (147)		2.337 (147)
120	2.294 (177)	2.303 (177)	2.317 (175)		2.313 (163)	
12-1		2.249 (183)		2.245 (192)		2.258 (182)
12-2	2.240 (196)	2.240 (196)	2.255 (196)	2.239 (199)	2.243 (195)	2.243 (199)

[a] $A_{\|}$ values (10^{-4} cm^{-1}) in parentheses. [b] See Table I. [c] This work. [d] Refs. 1 and 2. [e] Ref. 5. [f] Ref. 9.

secondary interaction with a protonated hydroxyl group (most likely HO-3, see above and ref. 5) as with the parent amino sugars. The stability of the (12-1) complex of α-ManN-OMe, in which one (NH_2,O^-) chelate ring is formed, is slightly higher than that of the corresponding complex of ManN (Table I). This finding suggests the same binding site for each complex, *i.e.*, the (NH_2,O-3^-) donors form chelate rings and the other ligand is bound through the amino group with co-ordination stabilised by additional interaction with protonated HO-3. At higher pH, the ligand is deprotonated and two identical (NH_2,O-3^-) chelates are formed, as with ManN (Table I). The slightly lower stability constant of the (12-2) complex of α-ManN-OMe, when compared to that of ManN, derives most likely from stronger steric interactions of the two ligand molecules with the more bulky glycoside. Increasing the pH above 8 may cause further deprotonations to form the species (12-3) and (12-4), as suggested by the potentiometric data. Deprotonation of the (12-2) complex to form the (12-3) species has already been suggested for the parent amino sugars (Table I, refs. 1,5,9). This process could involve the dissociation of a proton from another hydroxyl group of the ligand, possibly that interacting with the metal ion in its apical position[5]. However, the second deprotonation is unique for α-ManN-OMe. It is suggested tentatively that the deprotonating group is HO-6 and the (12-3) and (12-4) complexes involve O-6 of the ligands, assuming a distorted $^1C_4$ chair conformation.

*Copper(II)–methyl 2-amino-2-deoxy-α,β-*D*-galactopyranoside (αβ-GalN-OMe) system.* — The dissociation constant corresponding to deprotonation of the amino group is similar to those for all of the other amino sugar ligands presented in Table I. The series of copper(II) complexes found for this system is the same as that established for Cu(II)–β-GlcN-OMe (Table I, ref. 5) and, apart for the possible (12-3) complex formed at high pH, they are the same as the complexes presented for the Cu(II)–GalN system[9]. The species identified from the potentio-

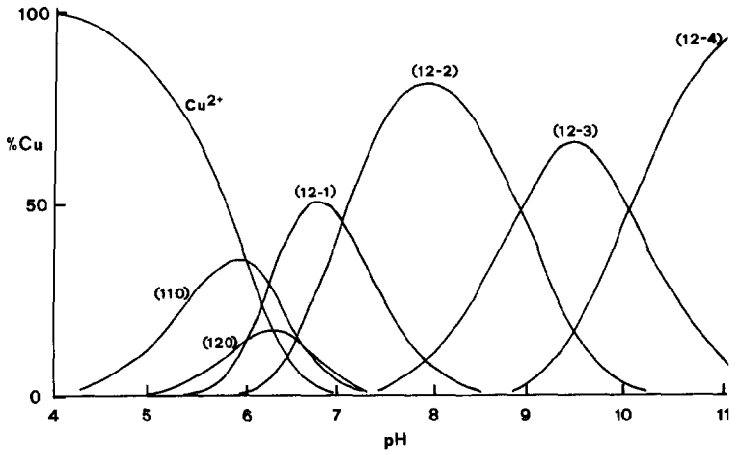

Fig. 3. Species distribution in the copper(II)–α-ManN-OMe system (4:1 ligand-to-metal ratio).

metric data are supported by the e.s.r. data (Table II). As with the β-GlcN-OMe ligand, the stabilities of the (110) and (120) species are lower than those of the GlcN or GalN complexes (Table I) as a result of the blocking of HO-1. However, the (110) species becomes the preponderant species at pH ~6.2 [40% of the total copper(II), Fig. 2], whereas the concentration of the (120) complex does not exceed 10% and its low proportion contributes to the large error in the stability constant calculated from the potentiometric data (Table I). However, the stabilities of the (12-1) and (12-2) complexes are almost the same as that of the corresponding GalN species (Table I). The lower stabilities of the (110) and (120) species formed by the methyl glycosides, when compared to the parent amino sugars, have been discussed above. The (110) complex of GalN is more stable than that of the αβ-GalN-OMe ligand [the stability constant for the GalN (110) complex calculated from the potentiometric data is not reliable due to its low concentration, and the more realistic polarographic value was used; Table I, see ref. 6]. The αβ-GalN-OMe (110) species appears to be slightly more stable than the corresponding complex of β-GlcN-OMe (Table I). Comparison of the stability of the (120) species is less realistic, as their concentrations in the copper(II)–glycoside systems are low and the stability constant may contain large errors. However, since the experimental conditions and the computer program used in the calculations were the same and the concentrations of (120) species, according to the calculations, were similar to each other, the resulting stability constants suggest that the complex with αβ-GalN-OMe is of higher stability than the species containing β-GlcN-OMe (Table I). The stabilities of both complexes having one or two (NH_2,O^-) chelate rings are considerably higher for the αβ-GalN-OMe ligand. Thus, blocking of HO-1 weakens considerably the binding ability of β-GlcN-OMe, whereas, with αβ-GalN-OMe, the chelated complexes have stabilities comparable to that of GalN. This behaviour suggests that the conformation of the GalN and/or αβ-GalN-OMe molecules may allow both HO-3 and HO-1 to compete in binding the metal ion. The high stabilities of both chelated complexes indicate that the availability of a hydroxyl group for chelation in αβ-GalN-OMe is almost the same as that in GalN or GlcN. Since, HO-1 is excluded from chelation, the most likely alternative is HO-3, although it is difficult to see why co-ordination through HO-3 should be significantly more favourable in GalN than GlcN. It is possible that formation of a complex with N and a vicinal O requires a change in the conformation of the ring, which will move both of these atoms away from the neighbouring substituents in the *α-galacto* structure but bring them closer in the *β-gluco* structure.

The results reported indicate that, besides the primary binding site at the amino nitrogen, deprotonated HO-1, HO-3, or even HO-4 (see ref. 5) can be involved in the co-ordination to cupric and other metal ions. No polynuclear complex was detected, perhaps because of the large excess of sugar used in the measurements.

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