1,5-Diaminopentanetriols and 1,6-Diaminohexanetetrols, Potent Dimer-forming Ligands for Cu^{2+} Ions. Potentiometric and Spectroscopic Studies

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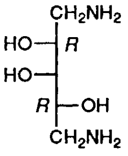
A series of diaminoalcohols (1,5-diaminotriols and 1,6-diaminotetrols) have been synthesised and their co-ordination abilities towards Cu^{II} studied by potentiometry and spectroscopic techniques (UV/VIS, EPR and CD). Both amino groups act as anchoring sites for two metal ions. Thus, two independent NH_2, O^- chelates are formed leading to dimeric complexes in which two metal ions are bound to two N-terminal atoms of the 1,5- or 1,6-diaminoalcohols. In all cases studied both ligand conformation and absolute configuration have a distinct impact on the stabilities of the complexes formed.

There is much of chemical and biochemical interest in metal complexes with a variety of amino polyalcohols. Aminoalcohols offer many possibilities for metal ion co-ordination, providing various N,O environments.[1–10] The structures of the complexes formed are monomeric and very often oligomeric with unusual physicochemical properties. Biologically, amino sugars, naturally occurring aminoalcohol analogues, may act as powerful ligands for metal ions like Cu^{II} with the amino group usually providing an efficient anchor for the metal ion.[1,5,9–12]

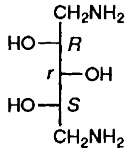
Recent work on the linear monoaminoalcohols (4-aminobutanetriols and 5-aminopentanetetrols)[11] has shown that although the nitrogen acts as an anchoring binding site the adjacent deprotonated hydroxyl groups act as bridges between two metal ions and have critical influence on the co-ordination equilibria, structures and stabilities of the complexes formed. The formation of alkoxide-bridged complexes seemed to be the most characteristic feature of these aminoalcohols. Diaminoalcohols may use two nitrogen donors as the anchoring sites for a metal ion and then the structures of the oligomeric species formed could be very different from those with monoaminoalcohols.[1] In this work we describe the co-ordination of Cu^{2+} to 1,5-diaminotriols and 1,6-diaminotetrols as studied by potentiometric and spectroscopic methods.

Experimental

Synthesis of Diaminoalcohols.—(2*S*,3*s*,4*R*)-1,5-Diaminopentane-2,3,4-triol (1,5-diamino-1,5-dideoxy-D-ribitol, *S*,*s*,*R*-L^1), (2*R*,3*r*,4*S*)-1,5-diaminopentane-2,3,4-triol (1,5-diamino-1,5-dideoxy-D-xylitol, *R*,*r*,*S*-L^1), (2*R*,3*R*,4*R*,5*R*)-1,6-diaminohexane-2,3,4,5-tetrol (1,6-diamino-1,6-dideoxy-D-mannitol, *RRRR*-L^2), (2*R*,3*R*,4*R*,5*S*)-1,6-diaminohexane-2,3,4,5-tetrol (1,6-diamino-1,6-dideoxy-D-glucitol, *RRRS*-L^2) and (2*R*,3*S*,4*R*,5*S*)-1,6-diaminohexane-2,3,4,5-tetrol (1,6-diamino-1,6-dideoxygalactitol, *RSRS*-L^2) were obtained as dihydrochlorides according to Kiely *et al.*[13] starting from the appropriate aldoses. (2*R*,4*R*)-1,5-Diaminopentane-2,3,4,-triol (1,5-diamino-1,5-dideoxy-D-arabinitol, *RR*-L') was obtained from 2,3,4-tri-*O*-acetyl-1,5-dichloro-1,5-dideoxy-D-arabinitol as described elsewhere.[14,15] Carbon-13 NMR, HPLC and potentiometry were used to check compositions and purity.



RR-L^1



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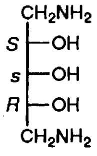

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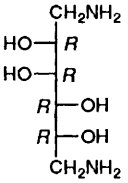
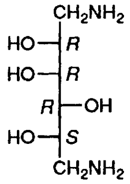
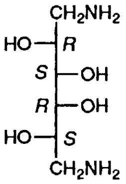


RRRR-L^2



RRRS-L^2



RSRS-L^2

Potentiometric Studies.—The stability constants of the complexes of H^+ and Cu^{2+} were calculated from pH-titration data obtained at 25 °C with a MOLSPIN automatic titration system. Changes in pH were monitored by using a glass–calomel electrode (Russell CMAWL) calibrated for hydrogen-ion activity. The relationship between activity and concentration was calculated daily by titration with HNO_3.[16] All solutions were prepared in 0.1 mol dm^{-3} KNO_3, the concentration of Cu^{2+} was 0.001 mol dm^{-3} and the metal-to-ligand molar ratio was 1:2, 1:3 or 1:4. Three titrations were performed for each system over the range pH 3–10 using volumes of 1.5 cm^3. Stability constants $\beta_{pqr} = [M_pH_rL_q]/[M]^p[H]^r[L]^q$ were calculated with the aid of the SUPERQUAD computer program.[17] The standard deviations reported were calculated by assuming random error.

Spectroscopic Measurements.—Absorption spectra were recorded on a Beckman DU 650 spectrophotometer, EPR spectra on a Bruker ESP 300E spectrometer at 120 K in the

Table 1 Proton dissociation constants (pK) and copper(II) complex-formation constants (log β) of diaminoalcohols at 25 °C and I = 0.1 mol dm^{-3} (KNO_3)

Species*		RR-L^1	RrS-L^1	SsR-L^1	$RRRR$-L^2	$RRRS$-L^2	$RSRS$-L^2
	log K_1	8.850	8.674	8.725	8.933	8.870	8.961
	log K_2	9.716(3)	9.623(2)	9.748(2)	9.761(1)	9.676(2)	9.764(2)
	log β_2	18.566(3)	18.297(1)	18.473(2)	18.694(2)	18.546(3)	18.725(3)
$Cu_2H_{-1}L_2$		16.29(8)	16.59(4)	15.34(1)	15.47(5)	16.47(3)	15.98(3)
$Cu_2H_{-2}L_2$		10.94(2)	10.85(1)	8.95(2)	9.87(1)	10.75(2)	9.90(2)
$Cu_2H_{-3}L_2$		2.64(5)	2.73(4)	1.43(6)	1.60(4)	2.69(5)	1.24(6)
$Cu_2H_{-4}L_2$		−6.98(8)	−6.94(5)	−7.45(9)	−7.89(6)	−6.52(6)	−8.53(7)
$Cu_2H_{-5}L_2$		—	—	—	−18.98(11)	−16.52(9)	−19.74(15)

* Charges omitted for simplicity.

X-band (9.3 GHz) with ethane-1,2-diol–water (1 : 2) as solvent and CD spectra on a JASCO 600 or on a Jobin Yvon 6CD spectropolarimeter. Concentrations used in the spectroscopic measurements were similar to those given above for potentiometric titrations.

Results and Discussion

The diaminoalcohols studied in this work behave as H_2L^{2+} type ligands. They possess two amino groups able to dissociate a proton in basic solutions with log K_1 8.67–8.96 and the more basic log K_2 9.62–9.76. Both amino functions are almost identical though the vicinal carbons may differ in their chirality. Comparison of different diastereoisomers, both in the 1,5-diaminotriols and 1,6-diaminotetrols, shows (Table 1) that the impact of different chiralities is negligible, if any. Both amino groups are well separated and the difference between pK_1 and pK_2 (around 0.8–1.0) is slightly higher than the statistical difference of 0.6 log unit. This may suggest the presence of some interaction between the two amino groups through water molecules. The same range of pK values was also found for 1,4-diaminobutanediols.[1]

Copper(II) *Complexes with* 1,5-*Diaminopentanetriols*.—The potentiometric data suggest the formation of dinuclear species only (Table 1, Fig. 1). This is strongly supported by the solution EPR spectra which reveal only the Cu^{2+} ion. All other complexes formed are EPR silent, indicating the formation of dimeric complexes with strong antiferromagnetic coupling between Cu^{2+} ions. The first complex formed, $[Cu_2H_{-1}L_2]^{3+}$, is a minor species and cannot be characterized by any spectroscopic method. The $[Cu_2H_{-2}L_2]^{2+}$ complex has well defined absorption and CD spectra (only RR-L^1 gives optically active complexes) (Table 2). The d–d transition energy around 620 nm indicates that each metal ion is co-ordinated to two nitrogen donors[18] and one deprotonated hydroxyl group.[1,18] The co-ordination mode is probably the same as that suggested earlier for 1,4-diaminobutanediol ligands.[1] The binding of amino groups results in an $NH_2 \rightarrow Cu^{2+}$ charge-transfer band around 300 nm (Table 2 for RR-L^1), while the bound deprotonated hydroxyl group gives another charge-transfer band at around 260 nm.[19] The lack of CD spectra for the complexes with RrS- and SsR-L^1 strongly supports the formation of the symmetric complexes (each metal ion has the same environment with opposite chirality on the closest carbon, Scheme 1).

Deprotonation of the $[Cu_2H_{-2}L_2]^{2+}$ species leads to drastic variations in the absorption spectra (Table 2). Proton dissociation from bound hydroxyl groups shifts the d–d transition energy towards higher values as expected. Also the $O^- \rightarrow Cu^{2+}$ charge-transfer band around 260 nm becomes more intensive (Table 2). The binding modes for all complexes obtained for 1,5-diaminopentanetriols are given in Scheme 1.

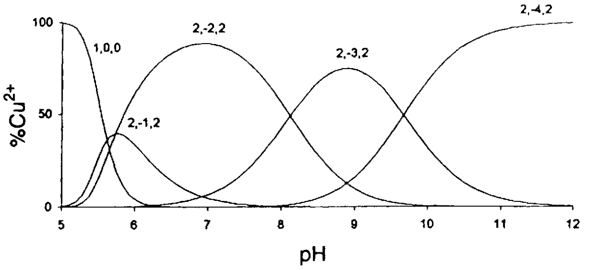
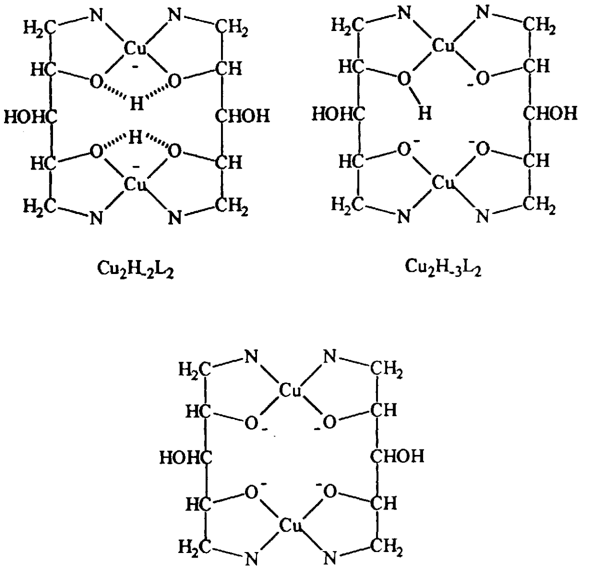


Fig. 1 Species distribution curves for Cu^{II}–RrS-L^1 complexes: c_{Cu} = 0.003 mol dm^{-3}, $c_L : c_{Cu}$ = 4 : 1; (1,0,0) corresponds to free metal ion



Scheme 1

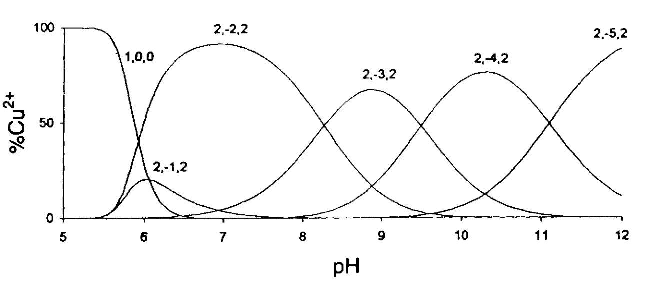


Fig. 2 Species distribution curves for Cu^{II}–$RRRR$-L^2 complexes; details as in Fig. 1

Table 2 Spectral parameters (UV/VIS, CD) for copper(II) complexes with diaminoalcohols (λ/nm; ε, Δε/dm^3 mol^{-1} cm^{-1})

	RR-L^1				*RrS*-L^1		*SsR*-L^1	
	UV/VIS		CD		UV/VIS		UV/VIS	
Species	λ	ε	λ	Δε	λ	ε	λ	ε
[$Cu_2H_{-2}L_2$]	608	64	627	+0.31	618	67	623	71
			326	+0.13				
			301	−0.04				
			264	+1.23				
[$Cu_2H_{-3}L_2$]	575	69	627	−0.05	572	66	575	78
			300	−0.18				
			262	+2.62				
			229	−1.01				
[$Cu_2H_{-4}L_2$]	580	67	625	−0.06	580	67	577	72
			302	−0.18				
			262	+2.60				
			230	−1.20				

	RRRR-L^2				*RRRS*-L^2				*RSRS*-L^2	
	UV/VIS		CD		UV/VIS		CD		UV/VIS	
Species	λ	ε	λ	Δε	λ	ε	λ	Δε	λ	ε
[$Cu_2H_{-2}L_2$]	610	60	641	+0.25	624	60	692	+0.09	636	59
			372	−0.13			585	−0.28		
			276	−2.14			282	+1.89		
			245	+2.20			233	−0.84		
[$Cu_2H_{-3}L_2$]	—	—	651	−0.18	620	57	686	+0.10	628	59
			370	−0.09			580	−0.19		
			275	−2.40			282	+1.73		
			244	+1.96			231	−0.81		
[$Cu_2H_{-4}L_2$]	608	59	640	+0.22	—	—	—	—	624	57
			376	−0.08						
			274	−2.17						
			243	+1.94						
[$Cu_2H_{-5}L_2$]	618	56	—	—	618	54	686	+0.11	628	54
							576	−0.20		
							280	+1.45		
							231	−0.60		

The impact of ligand chirality on the complex stabilities is clearly seen when complexes of the three diaminoalcohols studied are compared (Table 1). While the complexes with *RR*- and *RrS*-L^1 are very similar in stability, all species obtained with *SsR*-L^1 are around one to two orders of magnitude less stable than those obtained for the other two alcohols (Table 1).

Copper(II) *Complexes with* 1,6-*Diaminohexanetetrols*.—The chemical model obtained for the 1,6-diamino derivatives is the same as that discussed above for 1,5-diaminopentanetriols (Table 1, Figs. 1 and 2). The only difference is a [$Cu_2H_{-5}L_2$]$^-$ species obtained in potentiometric titrations of the 1,6 analogues at very high pH. This complex, however, should be treated as a minor species as its maximum concentration according to the calculations would be observed above pH 12 (see Fig. 2). Also in this case the formation of dinuclear complexes is supported by the lack of EPR spectra for all complexes except for free Cu^{2+}. The formation of symmetric dimers is strongly indicated by the lack of CD spectra for *RSRS*-L^2 which has opposite chiralities on the C^2, C^3 and C^5, C^4 pairs of carbons, which are involved in chelate-ring formation around two dimer-forming Cu^{2+} ions. Thus, metal ions bound to two amino sugar terminals contribute to CD spectra with opposite Cotton effects as is observed in the racemic mixture (see Scheme 1). The absorption and CD spectra are similar to those observed for the 1,5-diamino analogues, supporting the existence of two NH$_2$, O$^-$ coordination sets around each metal ion (Table 2). Comparison of the stabilities of the complexes formed by different diastereoisomers shows (Table 1) that also 1,6-diaminohexanetetrols are to some extent stereospecific. The most effective ligand is *RRRS*-L^2 with opposite chirality on carbons 2,4 and the same chirality on 3,4 (Scheme 1). Two other diastereoisomers form complexes with very similar stability except for those formed in basic solution, [$Cu_2H_{-4}L_2$] and [$Cu_2H_{-5}L_2$]$^-$, which are slightly more stable for the *RSRS*-L^2 isomer.

This indicates that proton dissociation from the [$Cu_2H_{-3}L_2$]$^+$ species (Scheme 1) is distinctly stereospecific. It is clearly seen when all three diaminoalcohols are compared (Table 1). The formation of the [$Cu_2H_{-5}L_2$]$^-$ species could result from proton dissociation from an axially bound water or one of the alcohol groups located between the two Cu^{2+} ions (C^3–OH or C^4–OH), or both simultaneously. However, both these processes are not very likely in the measurable pH range ($<$ 10.5) and this species is not treated here as a major complex (see above). Also very minor variations in the CD and absorption spectra during formation of [$Cu_2H_{-5}L_2$]$^-$ species do not confirm the formation of this complex.

Comparison of Monoamino- and Diamino-triols and -tetrols.—Our earlier work on monoamino-triols and -tetraols[11] showed that, similarly to the diaminoalcohols discussed above these form dimeric complexes of the same stoichiometry: [$Cu_2H_{-2}L_2$]$^{2+}$ to [$Cu_2H_{-4,-5}L_2$]$^{0,-1}$. However, the respective complex stability may differ by up to 10 orders of magnitude. This clearly reflects completely different binding modes occurring in both types of complexes. While dinuclear complexes formed by monoaminoalcohols contain one NH_2,O^- chelate and two Cu^{2+} ions are bound *via* two alkoxo bridges, in the case of diaminoalcohols each metal ion forms two NH_2,O^- chelates and both copper centres are held together by an alcohol carbon chain. Thus, the presence of two amino groups in diaminoalcohols serves as two anchoring co-ordination sites which allow the formation of two efficient chelate rings involving also the deprotonated neighbouring alcohol group. This leads to very stable dinuclear complexes. With both types of aminoalcohols, however, metal co-ordination is distinctly stereospecific.

Conclusion

Diaminoalcohols having two amino groups well separated from each other are very effective ligands for Cu^{2+} ions, forming stable dinuclear species. Each amino group acts as an anchoring site for one metal ion. Deprotonation of the neighbouring alcohol group leads to stable bis(chelates) which are linked by the carbohydrate chain to form dinuclear species. Similarly to monoaminoalcohols, the complex formation is a stereospecific process, although the structures and the stabilities of corresponding complexes of monoamino- and diamino-alcohols are completely different.

Acknowledgements

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