The Effects of Configuration and Ring Size on the Stability of Copper(II) Chelates of Amino Alcohols

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Abstract

The protonation constants and the successive stability constants of the copper(II) complexes of a series of amino alcohols were determined by means of potentiometric equilibrium measurements. The data reflected the effects of hydrogen-bonded chelate formation and the size of the ring formed on the protonation constants. The complex formation constants showed the effects of steric factors (*cis* or *trans* location of the donor groups, and size of the chelate ring) on the stabilities of copper(II) complexes and on the binding mode (mono- or bifunctional) of the ligands.

Introduction

Amino alcohols and their derivatives are physiologically important substances in animal and plant life processes. Alkaloids (e.g. ephedrin and derivatives) and antibiotics (e.g. streptomycin) belong in this family of compounds. Cyclic amino alcohols were prepared for pharmacologic and also stereochemical investigations [1–3]. Metallic copper served as catalyst in some heterogeneous processes used to prepare such compounds [4–6]. A knowledge of the copper complex formation equilibria could contribute to a better understanding of these catalytic methods. Unfortunately, the relevant literature contains data relating only to the simplest model compounds [7, 8], and some of the results are rather contradictory [9, 10].

The effect of the stereochemistry of *cis* and *trans* amino alcohols on the composition of their metal complexes was shown by preparative experiments of Drefahl *et al.* [11–13]. They did not study however the complex formation equilibria in solutions and could not get information therefore on the effect of the stereochemistry of the ligand on the stabilities of the complexes.

The comparison of metal complex formation equilibria by analogous ligands with different configurations (*cis* and *trans*) or which form similar chelates, but with different ring sizes (e.g. 2-amino-1-propanol and 3-amino-1-propanol), could contribute to the recognition of the basic principles influencing the metal ion coordination processes in this family of compounds. We have therefore performed an equilibrium study of the protonation and copper coordination of a series of amino alcohols (Table I). The results are discussed below.

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TABLE I. Protonation Constants (K_H) and Successive Stability Constants (K_1, K_2 and K_3) of the Copper(II) Complexes of the Studied Amino Alcohols

Ligand	$\log K_H$	$\log K_1$	$\log K_2$	$\log K_3$
2-amino-1-propanol (I)	9.07 ± 0.02	5.28 ± 0.02	3.99 ± 0.06	2.75 ± 0.1
2-amino-1-butanol (II)	9.05 ± 0.01	5.23 ± 0.02	4.33 ± 0.08	2.59 ± 0.3
3-amino-1-propanol (III)	9.77 ± 0.01	4.56 ± 0.03	4.21 ± 0.05	2.77 ± 0.1
cis-2-hydroxymethylcyclohexylamine (IV)	9.53 ± 0.04	5.65 ± 0.01	3.11 ± 0.05	3.0 ± 0.3
trans-2-hydroxymethylcyclohexylamine (V)	9.83 ± 0.01	5.06 ± 0.01	4.48 ± 0.05	3.6 ± 0.1
cis-2-aminomethylcyclohexan-1-ol (VI)	9.66 ± 0.05			
trans-2-aminomethylcyclohexan-1-ol (VII)	9.75 ± 0.04			

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Experimental

Materials

(±)-2-Amino-1-propanol (DL-alaninol) (**I**) and *R*(−)-2-amino-1-butanol (**II**) were FLUKA p.a. products.

3-Amino-1-propanol (**III**), *cis*-2-hydroxymethylcyclohexylamine (**IV**), *trans*-2-hydroxymethylcyclohexylamine (**V**), *cis*-2-aminomethylcyclohexan-1-ol (**VI**) and *trans*-2-aminomethylcyclohexan-1-ol (**VII**) were prepared according to refs. 14 and 15.

Equilibrium Measurements

Both protonation and copper coordination equilibria were investigated by means of potentiometric titrations in solutions of 2.00 cm^3 volume, using a G2222B Radiometer glass microelectrode and an OP-8201 Radelkis silver–silver chloride reference electrode. The titrations were performed with a computer-controlled online automatic titration device constructed in our laboratory [16]. A Radelkis OP-208/1 mV- and pH-meter served for the measurement of the EMF data (accuracy ±0.1 mV and 0.001 pH). The standard solution was added from a Radelkis OP-930/1 automatic burette. The two devices were connected through a laboratory-built interface to a Sinclair ZX-81 microcomputer of 16 K RAM capacity. A 8255 programmable interface transferred the BCD signals of the mV-meter to the computer and the command signals of the computer to the mV-meter and burette.

The computer not only operated the apparatus and ensured that only data corresponding to the equilibrium state were recorded, but also performed the online evaluation of the experimental data. Because of the low solubilities of the copper(II) complexes of the studied compounds, the equilibrium measurements had to be performed in a 1:1 water–ethanol solvent mixture. The use of this solvent instead of water in the measurements meant that the relative permittivities of the solutions, the autoprotolysis constant (K_W) of the solvent and the diffusion potentials in this system differed from those in a purely aqueous system. To obtain reliable equilibrium constants from the EMF measurements in the solvent mixture, the following relation was used between the experimental EMF values (E) and the equilibrium hydrogen ion concentrations ($[H^+]$):

$$E = E_o + 0.581 \log[H^+] + j_H[H^+] + j_{OH}[H^+]^{-1}K_W$$

where j_H and j_{OH} are fitting parameters in acidic and alkaline media for the correction of experimental errors, mainly due to diffusion potential differences; $K_W = 10^{14.3}$ is the autoprotolysis constant of the solvent, determined from titrations of standard 0.01 M perchloric acid solution with standard 0.01 M sodium hydroxide solution in the solvent mixture used in the investigations.

All measurements were performed in a 50 *v/v* % water–ethanol solvent mixture of 0.5 M ionic strength, made up with sodium perchlorate, at 20 ± 0.1 °C.

The protonation constants of the amino groups were determined through the potentiometric titration of 0.01 M amino alcohol solutions containing an equivalent amount of perchloric acid with standard 0.01 M sodium hydroxide solution.

Since copper ion coordination by amino alcohols in solutions of pH < 9 results in deprotonation of the amino groups, the stability constants of the copper complexes were determined in Calvin equilibrium deprotonation studies. The differences between the titration curves of copper ion-free and copper ion-containing ($[Cu^{2+}] = 2.5 \times 10^{-3}$ M) amino alcohol solutions (2.5×10^{-1} M) of identical $HClO_4$ content with standard sodium hydroxide (0.01 M) solution reflected the extent of proton release in the complex formation process. These data were used to calculate the Bjerrum complex formation functions of the complexes and the corresponding stability constants. This computer evaluation was performed on the basis of the Bjerrum complex formation function by means of a non-linear least square method. The reciprocals of the squares of the experimental data served as statistical weights in the square sums. The reproducibility of the equilibrium constants is illustrated in Table I.

As a check on the evaluation method, the computer simulated $\bar{n}$ *versus* log[A] curves (where [A] denotes the free ligand concentrations) and compared them with the corresponding experimental plots. The good agreement points to the reliability of the equilibrium constants. Figure 1 shows typical experimental and calculated Bjerrum formation curves for copper(II) coordination by **II**, **III** and **IV**.

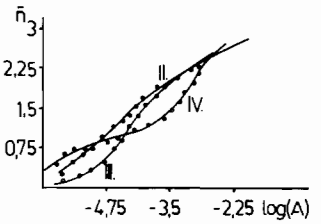

Fig. 1. Bjerrum complex formation curves for copper(II) coordination by amino alcohols **II**, **III** and **IV**. Circles denote experimental values; full lines are computer-calculated curves.

The percentage distributions of total copper(II) concentration in its different complexes were calculated for each system (Fig. 2). The stability constants and the corresponding distribution curves reflect the effects of configuration and chelate ring size on the complex formation processes.

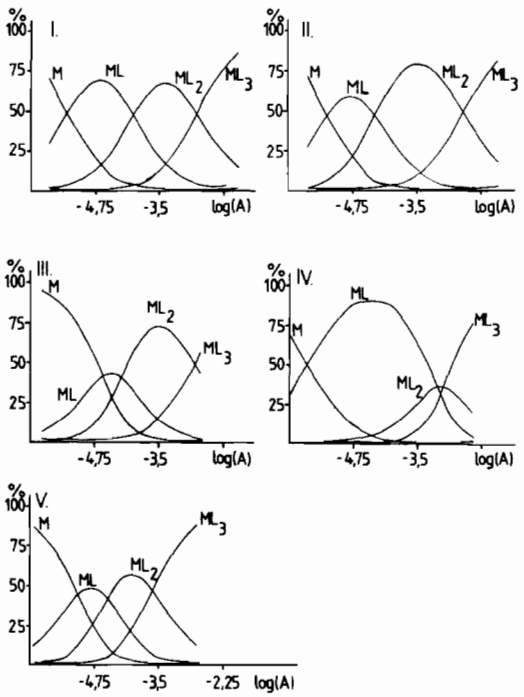

Fig. 2. Percentage distributions of total copper(II) concentration in its different complexes plotted as a function of the logarithms of free ligand concentrations. Roman numbers indicate the ligand as given in Table I. Total concentrations: copper(II) 2.5×10^{-3} M; amino alcohols 2.5×10^{-1} M.

Results and Discussion

The protonation constants and the stability constants (logarithmic values) of the copper(II) complexes of the investigated amino alcohols are presented in Table I.

The protonation constants (K_H) reflect the distance of the hydroxy group from the amino group in the ligand. The log K_H values of compounds **I** and **II**, in which these two functional groups are in vicinal position are significantly lower than those of the other ligands, where they are separated by three carbon atoms. This difference is due to intramolecular hydrogen-bonding between the amino and hydroxy groups in the amino alcohols. The binding of the proton of the hydroxy group to the amino nitrogen facilitates the deprotonation of the latter atom, giving the impression that its basicity is lower. This effect is enhanced by an increase in strength of the H-bond. Five-membered H-bonded chelate rings are formed in **I** and **II**, but six-membered rings in the other molecules. Steric factors favour the five-membered chelates. This is reflected in the smaller protonation constants of **I** and **II** than those of the other ligands.

The effect of the stereochemistry of the ligand on the H-bond in question is reflected in the log K_H values of the cyclic amino alcohols **IV**–**VII**. A comparison of the log K_H values of *cis* and *trans*-2-hydroxymethylcyclohexylamines shows that H-bond formation between the hydroxy and amino groups is more pronounced in the *cis* compound than in the *trans* one. A similar but less significant trend is seen for the *cis* and *trans*-2-aminomethylcyclohexan-1-ols.

From the above considerations it may be concluded that the protonation constants of these amino alcohols reflect the effect of H-bonded chelate formation rather than the electron density on the amino nitrogen atom. This suggestion is confirmed by the correlation of the protonation and complex stability constants; these indicate that, in contrast with general experience, in the present systems of ligand pairs with analogous compositions, but which form chelates with different structures (ring size or stereochemistry), the first successive complex stability constants decrease with increasing protonation constant of the ligand (compare, for example, K_1 for **I** and **III**, and for **IV** and **V**).

Compounds **I** and **II** form five-membered chelate rings with copper(II) ions; all the other ligands form six-membered chelates. Compounds **I** and **III** differ only in the positions of the functional groups on the propane chain. The pairs **IV** and **V**, and **VI** and **VII**, are the *cis* and *trans* isomers of the same molecules. (Unfortunately, the copper coordination of **VI** and **VII** could not be studied because of the low solubilities of their complexes even in the ethanol–water mixture.)

The log K_1 values in Table I and the distribution curves in Fig. 2 indicate that the first ligand coordinates bifunctionally in all systems. A comparison of the data on **I** and **III** reveals that the five-membered copper(II) chelates are more stable than the six-membered ones. The log K_1 values and corresponding distribution curves for **IV** and **V** show the preferential coordination of *cis*-2-hydroxymethylcyclohexylamine in the 1:1 complex.

The K_1:K_2 ratios are rather low (except that for **IV**) because of the high K_2 values, indicating that the second ligand is also coordinated bidentately to copper(II). In the case of **IV** (as reflected by the low value of K_2), the steric arrangement of the donor groups in the *cis* compound seems to hinder the chelation of the second ligand. The high K_2:K_3 ratios due to the low values of K_3 indicate that the third ligand is bound monofunctionally in each complex. Figure 2 reflects also these effects.

The effect of the rigidity imposed on the ligand by the cyclohexane ring is reflected in the differences in the stability constants of **IV**, **V** and **III**. These three ligands form six-membered chelate rings with copper(II) ions; **III** and **V** have similar protonation constants, but the stability constants of the copper complexes of **V** are significantly higher than those of **III**, because of the stabilizing effect of the cyclohexane

ring in **V**, which fixes the two donor groups of the ligand at the right distance for complex formation. In the case of the *cis* isomer of 2-hydroxymethylcyclohexylamine, the above effect promotes only the coordination of the first ligand, supporting the suggestion that the second ligand is bound monofunctionally.

The above considerations permit the conclusion that the complexes with maximum coordination number are pentacoordinated ones, except that of **IV**, which is probably tetracoordinated. For the direct determination of the symmetry of the coordination spheres, EPR studies are planned.

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