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# Copper(II) and zinc(II) complexes of betaxolol in methanolic solution

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## Abstract

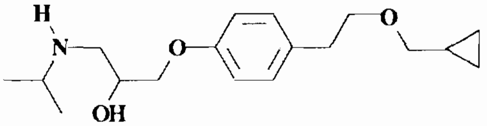
The complexation properties of betaxolol, a member of the large family of $\beta$-adrenergic blocking agents, were studied towards copper and zinc in methanolic solution. From the potentiometric and spectrophotometric results, the constants for the species $[CuL]_2^{2+}$ and $[CuOMeL]_2$ have been calculated to be log $\beta_{202}=22.51$ and log $\beta_{2-22}=-0.26$, respectively. The ligand, which contains an 1-aminopropan-2-ol moiety, forms a chelate via deprotonation and coordination of the alkoxide group. Furthermore, a second complex is formed by addition of a $CH_3O^-$ ion to $Cu^{2+}$. Near-UV and visible spectral parameters provide strong evidence for the presence of alkoxo-bridged binuclear species in solution, and it is likely that, as in the solid state, the complexes have a distorted square-planar structure. The zinc complexes are much less stable than those for copper, and without spectral characteristics; it is difficult to distinguish between the monomeric and dimeric model.

## Introduction

Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes. Probably the most widely studied cation in this respect is $Cu^{2+}$, since a host of low molecular weight copper complexes have proved beneficial in various diseases such as tuberculosis, rheumatoid arthritis, gastric ulcers and cancers. As a general rule, copper complexes show greater pharmacological activity and are less toxic than the ligand itself [1–4]. In addition to $Cu^{2+}$, other transition metal cations such as $Zn^{2+}$ have also often been considered. It therefore seemed interesting to study the complexation properties towards $Cu^{2+}$ and $Zn^{2+}$, of a member of the large family of $\beta$-adrenergic blocking agents commonly used in the treatment of hypertension and glaucoma.

Of further interest is the fact that the ligand under study contains an aminoalcohol moiety in its structure. Over the last few years, aminoalcohol–copper complexes have been the subject of numerous publications [5–13]. In particular, a large number of copper(II) complexes with aminoethanols and aminopropanols have been prepared [5–7, 11, 12]. Crystallographic studies as well as spectral and magnetic studies have shown that these complexes most often exist as di-alkoxo-bridged dimers in the solid state. The results in solution are however less clear, and diverse models have been proposed in which dimerization seldom occurs, and is somewhat difficult to prove [8, 9, 13].

The present work has been performed on betaxolol (see structure below),



which is the generic name for 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl]amino]-2-propanol (designated HL later on in the text). This compound has a relatively bulky isopropyl group attached to the amino nitrogen atom and a long hydrophobic chain at the other end of the molecule. The aim of this study is to see whether the structural features of this ligand lead to characteristic complexation properties, or whether properties similar to those found for other aminoalcohols are displayed.

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Due to the high lipophilicity of the basic form of the compound, the complexation studies were performed in dry methanol. In addition, compared to water, the solvating properties of this solvent result in less solvolysis of copper and zinc, and partial deprotonation of the hydroxyl group allowing the determination of its protonation constant. The latter is of particular importance since it enables the distinction between the two most likely models that have been proposed, i.e. solvolysis where a solvent molecule coordinated to copper is deprotonated, or chelation, where deprotonation leads to the coordination of the alkoxide group [8].

## Experimental

The solvent used for the potentiometric and spectrophotometric studies was dry methanol (Merck). In both cases, the ionic force of the solutions was kept constant at 0.1 mol dm$^{-3}$ by addition of NaCl. The titration reactant used throughout was sodium methoxide, prepared by reaction of sodium with methanol and further titrated with a sodium hydrogen phthalate solution of known concentration. Betaxolol hydrochloride was kindly provided by Alcon Research & Development and used without further purification. Metal solutions were prepared from anhydrous copper and zinc chloride (Aldrich Gold Label) and their concentrations determined by EDTA titration.

### *Potentiometry*

The protonation constants were determined by titration of a $5.00 \times 10^{-3}$ M solution of betaxolol with the base. For the complexation constants, a solution of copper or zinc ions was added to the ligand so that the metal to ligand ratio ranged from 0.2 to 0.5. The titrations were carried out in 25 cm$^3$ solutions at $25 \pm 0.1$ °C under an argon atmosphere, The p$H$ measurements were made with an Ingold glass electrode type HA 265 connected to a Tacussel Isis 20000 pH meter (p$H$ means the cologarithm of the concentration of $H^+$). The standard liquid in the reference electrode compartment was replaced with a methanolic solution of NaCl 0.1 mol dm$^{-3}$. The standardization of the electrode and the correction for the junction potential were carried out as previously reported [14]. The values of the constants $a$ and $b$ obtained are $a = 0.062$, $b = -6.20$. Data acquisition and control of the buret were performed by the program MICROPOT [15] which runs on an Apple II computer.

Both protonation and complexation constants were calculated using the program MINIQUAD [16]. In the case of the protonation constants, the number of weak acid groups on the molecule was first deduced from plots of the average degree of protonation, $\bar{p}$, versus p$H$. Overall protonation constants $\beta_{0yl}$ which refer to the equilibria

$$yH^+ + L^- \rightleftharpoons H_yL^{(y-1)+}$$

are given by the program MINIQUAD. [$L^-$] corresponds to the species having a deprotonated hydroxyl group.

The method used to determine the complexation constants is based on the method of competition between the metallic cation and the proton. Indications about the nature of the complexes along with approximative values of their stability constants were obtained from curves of $\bar{n}$ (mean number of ligands per metal) as a function of the free ligand concentration. During the data processing, the protonation constants were held constant and the value of p$K_{MeOH}$ was taken as 16.70 [17]. In the model used for the copper complexes, the solvolysis of $Cu^{2+}$ was taken into account, and the formation constant of $CuOMe^+$ ($Me = CH_3$) simultaneously refined. The final choice of the 'best' set of constants from the various combinations of species was mainly based on the residuals and the $R$ factor given by MINIQUAD. When, for each metal to ligand ratio, the calculation gave satisfying results, a final refinement was made including all the experiments. The overall stability constants $\beta_{xyz}$ given by the program characterize the following equilibria:

$$xM^{2+} + yH^+ + zL^- \rightleftharpoons M_xH_yL_z^{(2x+y-z)+}$$

### *Spectrophotometry*

Complexation of copper was studied on a Perkin-Elmer Lamda 5 spectrophotometer equipped with a thermostatted cell compartment set at 25 °C. Quartz cells with a 2 cm path length were used throughout. Spectra were recorded between 350 and 850 nm at a scan speed of 200 nm min$^{-1}$. Optical density values were taken at 25 nm intervals and used in the subsequent calculations. The solutions used in these experiments contained betaxolol hydrochloride $5.00 \times 10^{-3}$ mol dm$^{-3}$ and $CuCl_2$ $2.50 \times 10^{-3}$ mol dm$^{-3}$. After addition of sodium methoxide to the above solution, the p$H$ was measured under the same conditions as those used in the potentiometric experiments and the spectra then recorded. The p$H$ range studied was between 6.9 and 12.9. Spectra of the ligand and metal alone were also recorded under the same conditions to allow calculation of their extinction coefficients required in the interpretation of the results by LETAGROP-SPEFO [18]. This program allows the calculation of the stability constants of the different complexes in solution from spectrophotometric measurements.

## Results and discussion

The protonation constants of betaxolol are reported in Table 1. log $\beta_{011}$ and log $\beta_{021}$ refer to the hydroxyl and the amino groups of the molecule, respectively. In aqueous solution, due to the low acidity of the hydroxyl group, an accurate determination of the equilibrium constant that characterizes the protonation step of $L^-$ is not possible. Consequently, during complexation, it is difficult to attribute unequivocally the loss of a proton to either the hydroxyl deprotonation or to hydrolysis. The use of methanol as solvent enables such a distinction to be made. Under the concentration conditions used, the solutions contain up to 45% of $L^-$ for the highest pH (13.2). This percentage is obtained by calculating $\bar{p}$ the average degree of protonation.

The overall stability constants $\beta_{xyz}$ of the betaxolol–$Cu^{2+}$ and betaxolol–$Zn^{2+}$ systems are listed in Table 1.

For the copper cation, the complexes that form in methanol in the presence of NaCl at a concentration of 0.1 mol $dm^{-3}$ over the pH range studied, are $[CuL]_2^{2+}$ and $[CuOMeL]_2$. In italics are given the values of the constants obtained from the spectrophotometric measurements interpreted separately in both the visible (*) and near-UV (**) regions. The agreement between the potentiometric and spectrophotometric results is good for log $\beta_{202}$ and remains satisfactory for log $\beta_{2-22}$.

Despite the fact that the betaxolol–copper complex has been found to exist as a dimer alkoxo-bridged chelate in the solid state [19], such complexes were not at first expected in solution. Previous studies in aqueous solution on simple aminoalcohols have shown that for metal to ligand ratios equal to or less than one, successive ML, $ML_2$, $ML_3$ complexes along with some deprotonated or hydroxylated species tend to form [9, 13]. Except in the case of triethanolamine, dimers do not seem to be present [8, 13]. In this work, a large number of different models were tested during the calculation of the constants from the potentiometric and the spectrophotometric data. In both cases, it was not possible to differentiate between the two 'best' models, i.e. the dimer model which is mentioned above and its monomer equivalent. The inability to distinguish between monomeric and dimeric species in solution by potentiometric methods, even after using a series of different metal to ligand ratios, has been observed previously by Tauler *et al.* when high metal concentrations were not able to be used and the dimerization constant was unfavourable [8]. Nevertheless, both potentiometric and spectrophotometric methods rejected a model containing a mixture of monomers and dimers. The definitive choice of the species present in solution was, however, possible from spectral characteristics of the complexes which have been described previously in the literature [6, 7, 20].

The near-UV and visible spectra of the $Cu^{2+}$–betaxolol system ($C_L = 5.00 \times 10^{-3}$ mol $dm^{-3}$ and $C_M = 2.50 \times 10^{-3}$ mol $dm^{-3}$) are shown in Fig. 1. In the visible region, two isobestic points indicate equilibria between three species. In spectra 1–12, a decrease in absorbance at the higher wavelengths of the free copper cations coincides with the appearance of a green species which absorbs at 699 nm. In spectra 13–18, a purple complex forms with a broad peak at 570 nm as the green complex disappears. In the 350–450 nm region, the same trend is found again with peaks of higher intensities. The first three spectra do not pass through

TABLE 1. Overall stability constants of the complexes formed by copper and zinc with betaxolol. The stoichiometry of the complexes is given according to the general equation indicated in the text. *S* and *R* correspond, respectively, to the standard deviation of the residuals and the *R* factor given by MINIQUAD. *n* is the total number of experimental observations obtained in *N* experiments and used for the calculations. In italics are given the constants resulting from the spectrophotometric determinations in both the near-UV (*) and visible (**) regions

| Cation | *x* | *y* | *z* | log $\beta_{xyz} \pm \sigma$ | pH range | *N* | *n* | *S* | *R* |
|---|---|---|---|---|---|---|---|---|---|
| $H^+$ | 0 | 1 | 1 | 13.44 ± 0.01 | 9.7–13.2 | 3 | 104 | $5.7 \times 10^{-5}$ | 0.0090 |
|  | 0 | 2 | 1 | 24.07 ± 0.01 |  |  |  |  |  |
| $Cu^{2+}$ | 2 | 0 | 2 | 22.51 ± 0.02 | 6.9–11.75 | 5 | 175 | $3.5 \times 10^{-5}$ | 0.0070 |
|  |  |  |  | *22.79 ± 0.18** | 6.9–13.00 |  |  |  |  |
|  |  |  |  | *22.47 max 22.85*** |  |  |  |  |  |
|  | 2 | −2 | 2 | −0.26 ± 0.04 |  |  |  |  |  |
|  |  |  |  | *−0.75 max −0.54** |  |  |  |  |  |
|  |  |  |  | *−0.89 max −0.51*** |  |  |  |  |  |
|  | 1 | −1 | 0 | −8.31 ± 0.02 |  |  |  |  |  |
| $Zn^{2+}$ | 1 | 0 | 1 | 4.60 ± 0.02 | 9.0 ± 12.7 | 4 | 205 | $3.5 \times 10^{-5}$ | 0.0075 |
|  | 1 | −1 | 1 | −7.16 ± 0.02 |  |  |  |  |  |
|  | 2 | 0 | 2 | 12.51 ± 0.03 |  |  |  | $4.09 \times 10^{-5}$ | 0.0088 |
|  | 2 | −2 | 2 | −11.29 ± 0.03 |  |  |  |  |  |

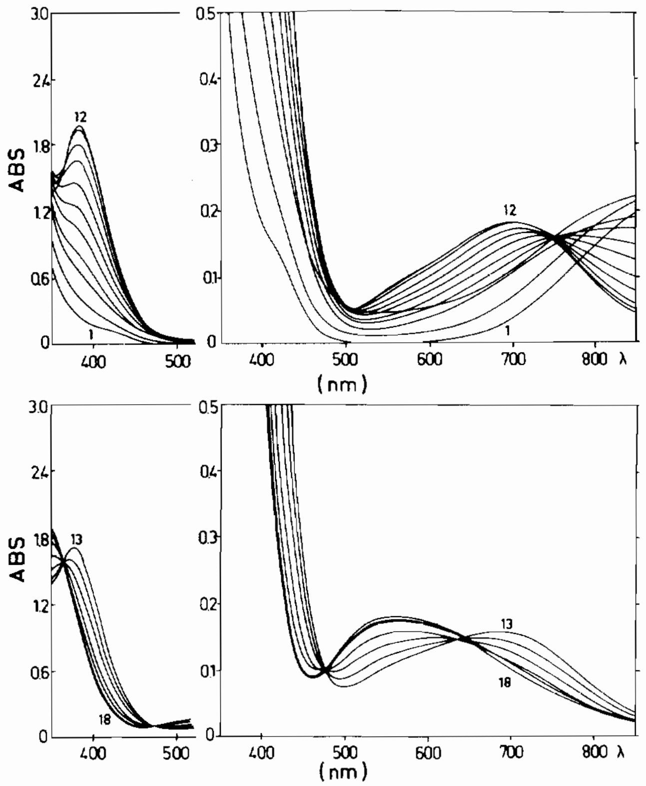

Fig. 1. Evolution of the near-UV and visible spectra of the $Cu^{2+}$–betaxolol system vs. pH ($C_L=5.00\times10^{-3}$ mol $dm^{-3}$; $C_M=2.50\times10^{-3}$ mol $dm^{-3}$). pHs are for spectra 1 to 18, respectively: 6.61; 7.72; 7.94; 8.11; 8.27; 8.45; 8.71; 9.32; 10.12; 10.53; 10.58; 11.15; 11.45; 11.76; 12.12; 12.50; 12.81; 13.00.

TABLE 2. Near-UV and visible spectral data of the $Cu^{2+}$–betaxolol complexes

| Complexes | | | | Band maxima (nm ($cm^{-1}$)) | | $\epsilon$ | |
|---|---|---|---|---|---|---|---|
| $x$ | $y$ | $z$ | Colour | UV | Vis | UV | Vis |
| 2 | 0 | 2 | green | 385 (26000) | 699 (14300) | 750 | 68 |
| 2 | −2 | 2 | purple | 350 (28600) | 570 (17500) | 695 | 69 |

the isobestic point due to the formation and slight precipitation of some copper methoxide salt. By raising the pH, redissolution is achieved.

The near-UV and visible spectral parameters obtained for the complexes are listed in Table 2. These parameters were obtained by treatment of the spectra (Fig. 1) by SPEFO. The most important region providing information about the nature of the species in solution is the near-UV region at about 27000 $cm^{-1}$. Two bands can be observed at 26000 and 28600 $cm^{-1}$ and are thought to correspond to the $[CuL]_2^{2+}$ and $[CuOMeL]_2$ complexes, respectively. Such bands can be attributed to charge transfer transitions from non-bonding orbitals of bridging oxygen atoms to the vacant *d* orbital on the copper cation [20]. These bands therefore provide strong evidence for the presence of alkoxo-bridged binuclear complexes in solution.

The lower absorption bands at 14300 and 17500 $cm^{-1}$ for both of the above complexes can be assigned to d–d transitions. According to Lindgren *et al.* [6], the position of these bands is consistent with complexes having a nearly square-planar structure. It would therefore seem likely that the complexes in solution display the same coordination geometry as those in the solid state, since a crystallographic study [19] has also shown the $[CuLBr]_2$ complex to have a distorted square-planar structure, where the plane is formed by the two alkoxo-oxygen atoms, the amino-nitrogen and the bromide anion.

In both the UV and visible regions the complex $[CuL]_2^{2+}$ absorbs at higher wavelengths than the $[CuOMeL]_2$ complex. This seems to indicate that the chloride ion is coordinated to copper in the first complex, whereas in the second it is replaced by a $CH_3O^-$ ion, resulting in a shift of the charge transfer band to higher energy. Such changes can be predicted from the spectrochemical series where the chloride anion is classified below the hydroxyl anion, which should be similar to methoxyl anion, in terms of ligand-field strength.

It seems, in addition, that neither the bulky isopropyl group on the nitrogen, nor the long hydrophobic chain hinder sterically the formation of the alkoxo-bridged binuclear copper complexes.

Figure 2(a) shows the distribution curves of the copper–betaxolol system ($C_L=5.00\times10^{-3}$ mol $dm^{-3}$ and $C_M=2.50\times10^{-3}$ mol $dm^{-3}$). The system appears to be quite simple with regard to other copper–aminopropanol systems previously investigated in aqueous solution. It can also be observed that, for the above concentration conditions, it would be possible to isolate the two complexes proposed by setting the pH to suitable values. Finally, the distribution of the solvated copper species is in agreement with its presence and subsequent redissolution when the pH increases.

The constants determined for the zinc–betaxolol system are listed in Table 1. Since the zinc complexes do not absorb like copper in the visible and near-UV region, it was not possible to distinguish, with the help of spectrophotometry, between the monomer and dimer models given by the potentiometric method. The *R* and *S* values of MINIQUAD are satisfactory, but do not differ significantly for the $ZnL^+$, ZnOMeL model and its dimeric equivalent. Even if, according to the Irving–Williams [21] rule, less stable complexes are expected for zinc than for copper, it is nevertheless surprising to see such large differences between the two sets of constants. It seems that for zinc the stereochemical requirements are difficult to be fulfilled with betaxolol, and for that reason the monomeric model may be more likely that the dimeric one.

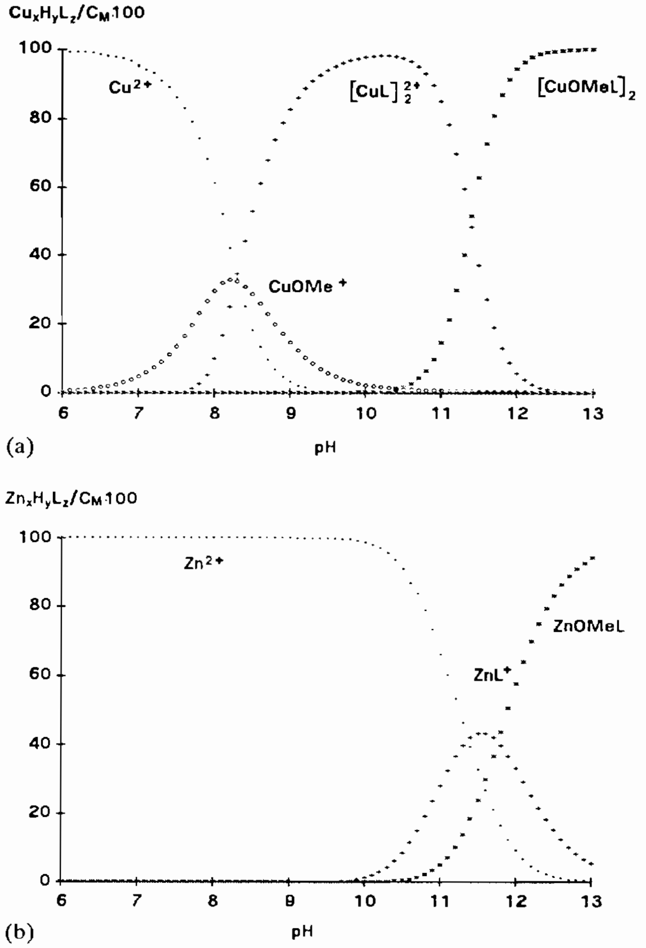

Fig. 2. Distribution curves of complexes of (a) the $Cu^{2+}$–betaxolol system and (b) $Zn^{2+}$–betaxolol system plotted against p$H$ in methanolic solution. $C_L = 5.00 \times 10^{-3}$ mol dm$^{-3}$ and $C_M = 2.50 \times 10^{-3}$ mol dm$^{-3}$.

Figure 2(b) displays the distribution curves of the zinc–betaxolol system for the monomeric model ($C_L = 5.00 \times 10^{-3}$ mol dm$^{-3}$ and $C_M = 2.50 \times 10^{-3}$ mol dm$^{-3}$). It appears that the complexation of zinc starts at higher p$H$ values (p$H > 10$ instead of p$H > 7.6$ for $Cu^{2+}$) and that in almost all the p$H$ range of complexation the $ZnL^+$ and ZnOMeL species do coexist.

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