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Complex Compounds of Cu(II) and Zn(II) with *N,N*-Dimethylglycine and *N,N*-Diethylglycine in Water and in Water—Methanol System

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The complex equilibria of the systems: copper—*N,N*-dimethylglycine, zinc—*N,N*-dimethylglycine, copper—*N,N*-diethylglycine, and zinc—*N,N*-diethylglycine have been studied by computer analysis of potentiometric data. The stability constants of the complexes formed in these systems are reported. A discussion is presented about the influence of the substituent and the solvent on the dissociation constants of the amino acids and the stability constants of their complexes with metals. ^{1}H NMR and IR studies indicate that both functional group of the ligands are involved in complex formation.

[Keywords: Copper(II); Complexes; N,N-Diethylglycine; N,N-Dimethylglycine; Zinc(II)]

Cu*(II)- und* Zn*(II)-Komplexe mit N,N-Dimethylglycin und N,N-Diethylglycin in Wasser und Wasser—Methanol-Lösung*

Anhand der Computer-Analyse von potentiometrischen Daten wurden die Bildungsgleichgewichte von Kupfer(II)- und Zink(II)-Komplexen mit *N,N*-Dimethylglycin und *N,N*-Diethylglycin untersucht. Die Beständigkeitskonstanten der gebildeten Komplexe wurden angegeben. Der Einfluß von Liganden und Lösungsmitteln auf Beständigkeit und Dissoziationskonstanten dieser Komplexe wurde diskutiert. Es wurde mittels ^{1}H-NMR- und IR-Untersuchungen festgestellt, daß bei der Bildung der Komplexe beide funktionellen Gruppen der Liganden teilnehmen.

Introduction

The complex formation reactions of amino acids with metals provide a useful model of metal—protein interactions. The both functional groups (amino and carboxylic) are potential coordination sites. The amino acid molecule may contain additional coordinating groups, such as the OH^- group in hydroxyproline or serine, or the second COO^- group in aspartic acid. The coordination process is also influenced by side chains which do not form direct coordinate bonds but which change the basic—acidic properties of the functional groups and modify the steric situation. For instance, substitution of a phenyl group at the glycine N atom results in a significant decrease of the basicity of the amino N atom. This effect in combination with steric hindrance leads to a considerable decrease of the stability of the complexes: in water—methanol systems the stability constants of Cu(II) complexes with *N*-phenylglycine are by about 4 and 3 log K units smaller (for M*L* and ML_2 species, respectively) than the corresponding values for unmodifide glycine[1]. This paper presents the results of the equilibrium studies of copper and zinc complexes with *N*,*N*-dimethylglycine (*DMG*) and *N*,*N*-diethylglycine (*DEG*). Most studies of these systems reported so far[2—6] assumed the M L_x species to be the only complexes formed. Neglection of other forms which might exist in aqueous solution (such as protonated species and hydroxy complexes) can lead to a false overall picture of the system and to wrong stability constants. Obviously, the *M*H*L* and *ML*OH forms do not exist in aprotic systems. In our previous work on copper complexes with *DEG* we found that in acetonitrile only Cu*L* and CuL_2 are formed[7].

The aim of this paper is to determine what complexes are formed in the investigated systems, what are their stability constants, and what is the influence of substituents and solvent on the complex formation reactions. To establish the mode of coordination in the investigated species also spectral measurements have been included.

Experimental

DMG (Fluka, Switzerland) was purified by recrystallization from anhydrous ethanol. It was dried and stored over P_2O_5. *DEG* (Na salt, Eastman Organic Chemicals, USA) was purified according to[7]. Copper and zinc perchlorates were obtained by dissolving CuO (BDH, England) and ZnO (POCh, Poland) in concentrated $HClO_4$ (Hopkin and Williams, England). The perchlorates were then crystallized and dried over P_2O_5. The solutions of $Cu(ClO_4)_2$ and $Zn(ClO_4)_2$ were calibrated by complexometric titration. Cu^{+2} was titrated using 0.050 *M EDTA* with glycylthymol blue as an indicator while for Zn^{2+} 0.010 *M EDTA* and methylthymol blue were applied.

Methanol (POCh, Poland) was dried using 3 A molecular sieves and then distillated.

In spectral studies the following deuterated compounds were used: D_2O (IBJ, Poland), DCl (PAN, Poland), NaOD (VEB-Berlin-Chemie), CD_3OD (USSR).

The *pH* was measured with a Radiometer GK 2401 C electrode and a Radiometer titrating set (*pH*-meter 26 c, autoburette ABU-1 c, titrator TTT 11, recorder SBR-2 c). The system was calibrated with two buffer solutions of

$pH = 4.005 \pm 0.005$ and 9.24 ± 0.01. The measurement were carried out at 21 ± 1 °C in the inert atmosphere of argon. The ionic strength $\mu = 0.1$ was adjusted with $NaClO_4$. The titrant was 0.173 *M* carbonate-free sodium hydroxide. Activity coefficients for water solutions were calculated according to *Davis*[8] whereas for water-methanol system they were estimated from E.M.F. measurements for a cell $Pt/H_2/HCl/AgCl/Ag$[9]. In order to be able to use the glass electrode for the determination of H^+ concentration in water—methanol systems the absolute calibration coefficients[10] were calculated

$$U_H^0 = \frac{\text{antilog}(-B)}{a_H}$$

where B is the pH-reading in mixed solvent system, $a_H = C_{HCl} \cdot f^{\pm}$, and C_{HCl} is the concentration of the HCl solution.

This method has been found applicable to the investigated systems up to 60% (*v*/*v*) methanol content. In aqueous systems the glass electrode response was checked according to a similar procedure.

The ligand concentrations in the stock solutions were 0.005 and 0.01 *M* while the metal concentrations were between 0.001 and 0.005 *M*.

The dissociation constants of both amino acids were determined in water and in solutions containing: 20, 30, 40, 50 and 60% (*v*/*v*) of methanol (the corresponding mole fractions of methanol are: 0.10, 0.16, 0.23, 0.31 and 0.40).

The stability constants of the metal—amino acid complexes were determined in water and in a solution containing 50% of alcohol. One or two equivalents (with respect to the ligand) of HCl were added to the solution prior to titration to shift the equilibrium to the desired region. The calculations included only the readings below the precipitation points.

The IR spectra were recorded in D_2O and in CD_3OD/D_2O on a Perkin-Elmer 180 spectrometer using CaF_2 cells. The ligand concentration as 0.2 *M*, and the ligand-to-metal ratios were 4 : 1, 2 : 1 and 1 : 1. The ^1H NMR spectra were recorded in D_2O and in CD_3OD/D_2O using a Varian EM-360 and BS 467 Tesla instruments with *DSS* as internal standard. The ligand concentration was 0.2 *M* and the ligand-to-metal ratios were from 2 000 : 1 to 10 : 1 in the case of copper, and from 5 : 1 to 1 : 1 in the case of zinc. The *pH* readings in D_2O and CD_3OD/D_2O were corrected according to the formula $pD = pH + 0.40$[11]. For all spectral measurements in the CD_3OD/D_2O systems, a solvent mixture containing 50% (*v*/*v*) of deuterated methanol was used. All calculation were carried out on a RIAD-32 computer using local version of the programs SCOGS[12], MINIQUAD[13], and HALTAFALL[14].

Results and Discussion

The central problems of the chemistry of complex equilibria i.e. the question of selection of the forms composing the system and of determination of their stability constants, have been solved by computer analysis of the potentiometric titration data using the programs SCOGS [12] and MINIQUAD[13]. Both these programs adopt the least-squares method to refine the overall formation constants of the complexes $M_pL_qH_r$ or $M_pL_q(\mathrm{OH})_s$:

$$\beta\,(M_pL_q\mathrm{H}_r) = \frac{[M_pL_s\mathrm{H}_r]}{[M]^p\,[L]^s\,[\mathrm{H}]^r}$$

and

$$\beta\,[M_p\,L_q(\mathrm{OH})_s] = \frac{[M_p\,L_q(\mathrm{OH})_s]\,[\mathrm{H}]^s}{[M]^p\,[L]^q}$$

A number of criteria have been proposed so far to test the correctness of the selection of the complex forms present in an equilibrium system[15—17].

A valuable additional test may be to compare the values of the stability constants obtained from SCOGS and MINIQUAD. It has been found that for correctly solved systems the differences between the corresponding values calculated by these two method are not significant according to one—parameter significance test[18].

The two investigated amino acids are potentially bidentate ligands and behave in both water and water-methanol as dibasic acids.

The titration curves of both *DMG* and *DEG* exhibit clearly distinguishable inflection points at $a = 1$ (a — moles of the titrant base per mole of the acid) corresponding to neutralization of the carboxylic group. Neutralization of the "ammonium proton" of the zwitterion molecules takes place at much higher *pH* (basic conditions) and the second inflection point is very unclear.

Table 1 reports the dissociation constants determined in water and in water—methanol. It shows that a change of the substituent influences pK_2 to a much higher degree than pK_1. This phenomenon is explained by the fact that the substituent is located at the amino group, the dissociation of which corresponds to pK_2. A past from the differences in pK_2 due to the inductive effect, Table 1 also shows that the basicity of the carboxyl group in *DEG* is somewhat higher and that it increases with the molar fraction of alcohol.

The changes of pK_2 in the series: glycine → *N*-methylglycine → *N*,*N*-dimethylglycine → *N*,*N*-diethylglycine are quite unexpected and difficult to interpret. The basicity of the amino group in *N*-methylglycine is higher than in glycine[1], but introduction of the second methyl substituent results in a decrease of the basicity. Introduction of two ethyl substituents, however, leads to an appreciable increase of the basicity of $-\mathrm{NH}_2$.

For both amino acids studied in this work an increase of the molar fraction of methanol (and the corresponding decrease of the dielectric constant of the solvent) reduces the pK_2values and increases the pK_1 constants. The amino acids contain two different acid/base systems: (i) $-\overset{+}{N}H_3/-NH_2$ with the proton covalently bonded to the N atom and (ii) $-COOH/-COO^-$ in which the bond is in an appreciable degree of ionic character. Consequently, when the dielectric constant is lowered, the increase of the interaction between the proton and the negalively charged carboxyl O atom is larger then the increase of the ion-dipol interaction between the proton and the solvent molecule. As a result, the pK_1 value is increased. Conversely, at lower dielectric constant the increase of the ion-dipol interaction between the proton and the solvent is more pronounced than the increase of the interaction between the proton and the amino N atom, and in consequence the pK_2 value becomes smaller. The differences in the character of these two groups are also reflected in the magnitudes of the changes of the dissociation constants. In the investigated range of methanol content pK_1 changes by 0.4 units for *DMG* and 0.2 units for *DEG*. The corresponding changes of pK_2 are 0.8 and 1.0.

Table 1. *Dissociation constants of amino acids in water and in mixed solvent*

Mole fraction of methanol	Amino acid *DMG* pK_1	*DMG* pK_2	*DEG* pK_1	*DEG* pK_2
0	1.90	9.77	1.93	10.54
0.10	2.10	9.53	2.15	10.47
0.16	2.23	9.49	2.32	10.43
0.23	2.40	9.45	2.51	10.40
0.31	2.55	9.40	2.70	10.36
0.40	2.73	9.37	2.95	10.34

Similar relations were reported for a number of systems with O—H and N—H bonds[19].

The hypothesis of the crucial influence of the dielectric constant on the dissociation constants is supported by the linear relation between pK_1 and $1/D$ (Fig. 1). (This relation is approximatelly also fulfilled for pK_2.)

Table 2 presents the stability constants of the complexes formed by *DMG* and *DEG* with zinc and copper.

Zinc reacts with *DMG* to yield ZnL, ZnL_2 and ZL_2OH species both in water and in water—methanol. These complexes are more stable in the water—methanol system. The program HALTAFALL[14] was used to calculate the distribution of metal between the various complex forms as

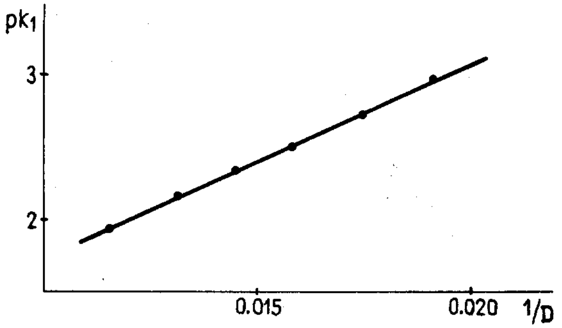

Fig. 1. Dependence of pK_1 of *DEG* upon the reciprocal of dielectric constant

Table 2. *Overall stability constants of copper(II) and zinc(II) complexes with DMG and DEG*

Solvent	*DMG*	log β	*DEG*	log β
H_2O	CuL	7.00 (4)	CuL	7.34 (7)
	CuL_2	13.33 (5)	CuL_2	13.70 (8)
	Cu(HL)L	18.20 (3)	CuHL	12.06 (9)
	CuLOH	−2.50 (9)	CuL_2OH	3.03 (24)
	ZnL	3.58 (5)	ZnL	4.77 (11)
	ZnL_2	6.99 (6)	ZnLOH	−2.91 (4)
	ZnL_2OH	−3.88 (10)		
CH_3OH/H_2O 50%/50% (*v*/*v*)	CuL	7.32 (3)	CuL	7.68 (9)
	CuL_2	13.78 (4)	CuL_2	14.34 (15)
	Cu(HL)L	18.23 (8)	CuHL	12.30 (8)
	CuL_2OH	2.51 (9)	CuL_2OH	4.11 (16)
	ZnL	4.45 (3)	ZnL	5.08 (9)
	ZnL_2	8.16 (4)	ZnLOH	−1.80 (9)
	ZnL_2OH	−2.40 (12)		

a function of *pH*. The complexes in the *DMG*/Zn system begin to form in water at *pH* ~ 6.4 and in water—methanol at *pH* ~ 5.7. In the case of the *DEG*/Zn system in both solvents only ZnL and ZnLOH species are formed. Due to higher basicity of the $-NH_2$ group the complexes with *DEG* are more stable than the compounds formed with *DMG*, although steric hindrance must be an unfavorable factor in the case of the *DEG* ligand. Complex formation in the *DEG*/Zn system starts in water at *pH* ~ 5.8 and in water—methanol at *pH* ~ 5.2. To determine the coordination sites for both *DMG*/Zn and *DEG*/Zn, the ^{1}H NMR spectra of the nonlabile protons (methyl and methylene) have been recorded. In the spectrum of the *DMG* zwitterion measured in D_2O the signals of the $-CH_3$ protons are located at 2.87 ppm while the methylene protons absorb at 3.65 ppm (in CD_3OD/D_2O the respective values are 2.87 and 3.62 ppm). Introduction of Zn^{2+} shifts the signals to 2.84 and 3.57 ppm (in CD_3OD/D_2O to 2.71 and 3.42 ppm). In view of the distribution of the nonlabile protons in the *DMG* molecule these changes are interpreted as attesting to the participation of both functional groups of the molecule in complex formation. This conclusion is supported by the observation that the signal from the methylene group (which is located between the two functional groups) shifts more than the signal from the methyl group.

Additional evidence of the engagement of the carboxyl group in complex formation comes from the IR spectra. In the IR spectrum of free *DMG* the characteristic band due to asymmetric stretching vibrations of the carboxyl group appears at 1 628 cm^{-1} in D_2O solution and at 1 632 cm^{-1} in CD_3OD/D_2O. Interaction with the cation shifts this band to lower wave number. This phenomenon can be attributed to the metal—carboxyl oxygen band formation and it has been observed for all systems discussed in this work.

For the *DEG* zwitterion the following signals are observed in water solution: 1.28 ppm (triplet from methyl protons, $J = 7.2$ Hz), 3.25 ppm (quartet from the "ethyl" methylene group, $J = 6.8$ Hz), 3.67 ppm (singlet from the "glycine" methylene group). (The corresponding values in the water—methanol system are: 1.27 ppm, $J = 7.2$ Hz; 3.25 ppm, $J = 6.7$ Hz; 3.68 ppm.) In the *DEG*/Zn system these signals are shifted to 1.25, 3.23 and 3.75 ppm (similar changes are observed in both D_2O and the CD_3OD/D_2O solvent). The biggest change is observed for the "glycine" methylene protons which are located between the two functional group. Therefore also in this system coordination involves both functional groups. (The IR spectra support this conclusion.)

The identical coordination modes in both systems (*DMG*/Zn and *DEG*/Zn) provide further evidence that the higher stability of the *DEG* complexes is related to the increased basicity of the *DEG* functional groups and not to structural changes.

The character of the equilibria in the *DMG*/Cu and *DEG*/Cu systems is more complicated. *DMG* reacts with copper to form Cu*L*, CuL_2 and Cu(H*L*)*L* in both solvent systems and also Cu*L*OH in water and CuL_2OH in CH_3OH/H_2O. The complexes begin to form at *pH* ~ 3.0 in water and *pH* ~ 2.6 in the mixed solvent system. It should be noted that in the Cu(H*L*)*L* complex one of the ligands is the deprotonated *DMG* anion while the other is the *DMG* zwitterion. *DEG* forms with copper in both solvents the following complexes: Cu*L*, CuL_2, CuH*L*, and CuL_2OH. In CuH*L* the metal ion is monodentately coordinated by the zwitterion form of the amino acids. The bonding site is the carboxyl group since the amino function group is blocked with the proton. A diagram showing the distribution of the metal between various complex forms vs. *pH* (Fig. 2) indicates that complex formation of *ML* species in the *DEG*/Cu system starts at *pH* ~ 3.3 in water (in CH_3OH/H_2O solvent at *pH* ~ 2.9). (Percentages for metal-containing forms refer to total metal, and for metal-free forms to total ligand.)

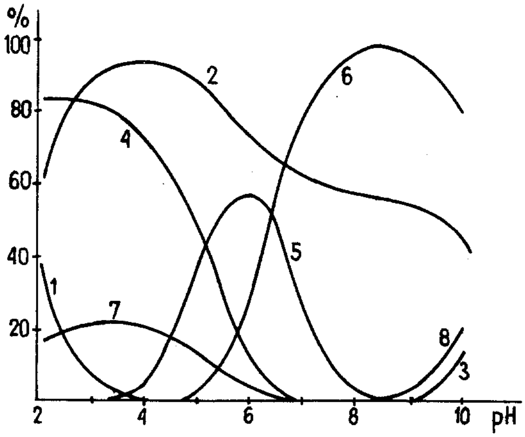

Fig. 2. Distribution diagram of the *DEG*/Cu system in water. *1* H_2L; *2* H*L*; *3* *L*; *4* *M*; *5* *ML*; *6* ML_2; *7* *M*H*L*; *8* ML_2OH

To determine the coordination sites in the Cu complexes the ^{1}H-NMR and IR spectra of the *DMG*/Cu and *DEG*/Cu systems have been recorded. Fig. 3 is an example of the results showing the ^{1}H-NMR spectral changes due to complex formation in the *DEG*/Cu systems in D_2O solution. The signal from the methyl protons moves to 1.23 ppm, that from the "ethyl" methylene protons to 3.20 ppm, and that from the "glycine" methylene group to 3.77 ppm. At the same time the signals become broader, particularly that for the "glycine" methylene protons (this signal disappears first when the Cu^{2+} concentration is increased). These observations (one should keep in mind the limitations due to the paramagnetic properties of the Cu^{2+} ion[20]) along with the shift of the IR band corresponding to the asymmetric vibration of the $-COO^-$ group attest to the participation of both functional groups in complex formation. The same is true for all investigated systems containing Cu^{2+}. Similarly as in the case of zinc containing systems, the complexes with *DEG* are more stable than those with *DMG* and the stability of the complexes in CH_3OH/H_2O is higher than in water. Therefore, also in this case the basic—acidic properties of the functional group are the main factor determining the stability of the complexes.

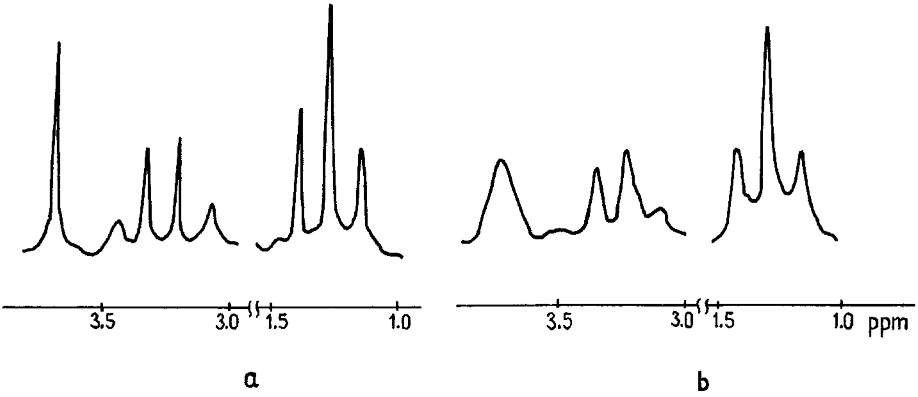

Fig. 3. ^{1}H-NMR spectra of *DEG* in D_2O (a), $pD = 6.8$ and of *DEG*/Cu in D_2O (b), $pD = 6.8$; $C_{DEG} = 0.2\,M$, $C_{Cu} = 0.002\,M$

From the distribution diagrams of the metal the reaction pathways leading to the hydroxy complexes have been deduced. The $MLOH$ species are formed in the reaction $ML + OH^- \rightleftharpoons MLOH$ but to same extent also in the reaction $ML_2 + OH^- \rightleftharpoons MLOH + L$. The precipitation of metal hydroxides observed at high *pH* attests to the competition between OH^- and the investigated ligands. Therefore, the intermediate form between the ML_x complex and the metal hydroxide is the $ML_y(OH)$ species. From similar analysis of the concentration of the complexes vs. *pH* it has been concluded that the protonated $Cu(HL)L$ species in the *DMG*/Cu system is formed in the reaction: $CuL + HL \rightleftharpoons Cu(HL)L$.

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