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Complexing Properties of Methyl and Phenyl Glycine Derivatives in their Compounds with H^+, Ni(II), Cu(II), and Zn(II)

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The influence of the solvent and the substituents on the complexing properties of methyl and phenyl glycine derivatives is discussed. On the basis of a computer analysis of potentiometric titration results, the composition and the stability constants of the complexes of *N*-methylglycine, *N,N*-dimethylglycine, *N*-phenylglycine and phenylglycine with H^+ and with Ni(II), Cu(II), Zn(II) were determined. The ligand-metal coordination mode as well as the zwitterion level in percent in ligand/proton systems were determined by spectral analyses and equilibria studies.

(Keywords: Copper(II); Complexes; Glycine Derivatives; Nickel(II); Zinc(II)]

Komplexbildung der Methyl- und Phenylglycin-Derivate in ihren Verbindungen mit dem Proton und Ni(II), Cu(II) *und* Zn(II)

Der Einfluß des Lösungsmittels und der Substituenten auf die komplexbildenden Eigenschaften der Methyl- und Phenylglycin-Derivate wird diskutiert. Anhand einer Computer-Analyse von potentiometrischen Daten wurden die Zusammensetzung und die Beständigkeitskonstanten der Komplexe von *N*-Methylglycin, *N,N*-Dimethylglycin, *N*-Phenylglycin und Phenylglycin mit H^+, Ni(II), Cu(II) und Zn(II) festgestellt. Mittels spektroskopischer Methoden und Gleichgewichtstudien wurde der Koordinationstyp des Liganden mit dem Metall festgestellt sowie der Prozentanteil des Zwitterions im Ligand/Proton-System.

Introduction

Amino acids as protein components play a crucial role in intra-cellular processes of living organisms. A number of reactions that occur in the course of biochemical processes involve metal ions. The metal—amino acid interaction can be treated as a model reaction of the metal—protein

system. In studies of complexing equilibria of systems with amino acids, their alkyl, and especially aryl derivatives have been treated only marginally[1—8]. The amino acid—metal bond formation reactions were studied almost exclusively in aqueous medium. Results of studies carried out in non-aqueous media, and particularly in mixed solvents concern only a limited number of ligands[9—12].

The results of research on complexing equilibria of nickel(II), copper(II), zinc(II) and H^+ with *N*-methylglycine (*SARK*), *N,N*-dimethylglycine (*DMG*), *N*-phenylglycine (*N-PHEN*) and phenylglycine (*PHEN*) in water and water-methanol solution are given in the present paper. The aim of the study is to determine types of complexes formed in the system as well as their stability and the influence of substituents and solvent on the nature of complexing equilibria.

Experimental

The following compounds were used in the study: *N*-methylglycine, *N,N*-dimethylglycine, *N*-phenylglycine and phenylglycine (Fluka, Switzerland). Perchlorates of nickel, copper and zinc were obtained by dissolving metal oxides in concentrated $HClO_4$. Potentiometric titration was carried out on a *pH*-meter, PHM-26 c-Radiometer. IR spectra were obtained on a Perkin-Elmer spectrophotometer, Model 180, ^{1}H-NMR spectra by means of a Varian EM 360 and a BS-467 Tesla spectrometer, ^{13}C-NMR spectra on a JEOL Fx 90 Q FT spectrometer. Details concerning experimental procedure were given earlier[13—16]. The types of complex compounds formed in the investigated systems as well as their stability constants were determined by a computer analysis of potentiometric titration results. The programs SCOGS[17] and MINIQUAD[18] were used. Calculations were performed on a RIAD-32 computer. The metal distribution among different forms of complex compounds was calculated using the program HALTAFALL[19]. The participation of a zwitterion in ligand/proton systems in water and water-methanol solvent (50%/50% *v/v*) was determined on the basis of chemical shift measurements in NMR of non-labile protons (from $—CH_3$ and $—CH_2$ groups) as a function of hydrogen ion concentration. The position of signals is dependent on a change in the screening of these protons, caused by the protonation of neighbouring functional groups. After adding acid to the anion $R—NH—CH_2—COO^-$, each of the acid-base groups adds for some time D^+, exposing the neighbouring, non-labile protons to an extent depending on the nature of functional groups, the distance, and time fraction in which the group is protonated. The resulting change in chemical shift is as follows[20]:

$$\Delta\delta_i = \sum_{j=1}^{n} C_{ij} f_j \tag{1}$$

where $\Delta\delta_i$ is the change in the chemical shift of the *i*-th signal, C_{ij} is the constant expressing the change in chemical shift of the *i*-th signal as a result of protonating the *j*-th group, and f_j is the time fraction of protonating the *j*-th group.

Thus in the studied ligand the change in the chemical shift of the methylene group protons is the sum of the protonation effects of the carboxylic and amino groups.

$$\Delta\delta_{CH_2} = C_{RHN}f_{RHN} + C_{COO}f_{COO} \quad (2)$$

whereas for protons of the methyl group:

$$\Delta\delta_{CH_3} = C_{RHN}f_{RHN} \quad (3)$$

Fig. 1 presents an example of NMR signal position shifts as a function of *pD*. After solving the equation systems (2) and (3) and using the established chemical shift values, the participation of the zwitterion was calculated in the analyzed system.

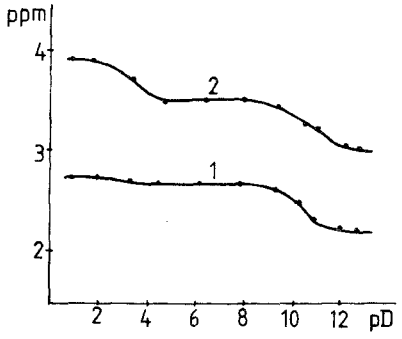

Fig. 1. ^{1}H-NMR chemical shifts for methyl (curve *1*) and methylene protons (curve *2*) of *N*-methylglycine in D_2O/CD_3OD 50%/50% *v/v* as a function of *pD*

Results and Discussion

As was stated earlier for successive glycine derivatives[13—16], a distinct systematic change in complexing properties of methyl and phenyl derivatives of glycine can be established. A ligand-proton as well as a metal-ligand bond stability change is observed. Table 1 presents the dissociation constants of the studied amino acids in water and water-methanol solution. Both for glycine and its methyl and phenyl derivatives a pK_1 increase is observed, as well as a decrease of the amino acid pK_2 value with the increase of the methanol mole fraction. A detailed discussion of the influence of substituents and solvent on dissociation constant values is given in Refs.[13—16]. Analyzing the data presented in Table 1, it should be noted that the greatest substituent effect is observed in *N*-phenylglycine, where the pK_2 value is about four orders of magnitude lower than in glycine, the pK_1 value being at the same time the lowest in the studied series of amino acids. Comparing both phenyl derivatives, the pK_1 value difference of both compounds increases clearly with the increase of the organic solvent mole fraction. It is a characteristic phenomenon that the introduction of two methyl groups (as in *DMG*) has a lesser effect on the pK_2 value change in relation to glycine compared with the case of substituting a —CH_3 group (as in *SARK*). The pK_1 values of both methyl derivatives decrease with the increase in the number of —CH_3 groups.

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

Amino acids	Glycine		*SARK*		*DMG*		*N-PHEN*		*PHEN*	
mole fraction of methanol	pK_1	pK_2	pK_1	pK_2	pK_1	pK_2	pK_1	pK_2	pK_1	pK_2
0	2.40	9.61	2.22	10.05	1.90	9.77	—	—	1.61	9.14
0.10	2.70	9.48	2.44	9.93	2.10	9.53	1.78	4.95	1.81	9.10
0.16	2.81	9.46	2.52	9.88	2.23	9.49	1.85	4.93	1.99	9.07
0.23	2.99	9.41	2.67	9.81	2.40	9.45	1.92	4.89	2.18	9.06
0.31	3.17	9.35	2.82	9.77	2.55	9.40	2.02	4.83	2.44	9.05
0.41	3.40	9.30	3.01	9.70	2.73	9.37	2.10	4.80	2.72	9.01

Moreover, it should be noted that the pK_1 value changes of both methyl derivatives of glycine are less distinct than changes resulting from the substitution of phenyl groups (in *PHEN* and *N-PHEN*).

Depending on conditions, the analyzed ligands occur in different ionic form. An increase in the mole fraction of CH_3OH in the system leads to a decrease in percentage of the zwitterion that plays a decisive role in the metal complexing process. After solving the dependences of chemical shift changes on *pD* (presented above), it was found that in water *SARK* occurs in 94% in the form of the zwitterion, whereas in the water-methanol system (50%/50% *v/v*) in 91%. In the case of *DMG* the zwitterion level decreases to 92% in water and 89% in the mixed solvent. A solvent of a given "ionizing power", depending on its dielectric constant *D*, affects the O—H bond and the covalent N—H bond to a different extent. A rise in the *D* value increases the probability of an oxygen-hydrogen bond cleavage which is characterized by a stronger electrostatic interaction (compared to N—H). Consequently, a preference for the occurrence of the amino acid in the zwitterionic form is observed in solutions having a higher dielectric constant. The presented results confirm this statement. Comparing both amino acids (*SARK* and *DMG*) in the same medium, sarcosine demonstrates a stronger tendency to occur in the zwitterion form despite a less labile carboxyl proton. On the other hand, however, the amino group of *SARK* exhibits a higher basicity in relation to *DMG* and that facilitates the formation of a $-(R)\overset{+}{N}H_2$ group. It must be added that the dependence of chemical shifts on *pD* can be utilized for calculations under two necessary assumptions: (i) the order of screening changes is linearly dependent on the time fraction of protonating the *j*-th group and (ii) the effect of the protonation of two neighbouring groups is additive. The arrangement of the protons in the molecule makes it impossible to carry out a similar analysis for *N*-phenylglycine and phenylglycine.

Table 2. *Stability constants of N-methylglycine complexes with* Ni(II), Cu(II) *and* Zn(II) *in water and water-methanol solvent*

Solvent	Metal	Reaction	$\log\beta$
H_2O	Ni	$M + L \rightleftharpoons ML$	5.42 (3)
		$M + 2L \rightleftharpoons ML_2$	9.87 (3)
	Cu	$M + L \rightleftharpoons ML$	7.83 (1)
		$M + 2L \rightleftharpoons ML_2$	14.57 (2)
		$M + L + H^+ \rightleftharpoons MHL$	11.49 (4)
		$M + L + H_2O \rightleftharpoons MLOH + H^+$	−0.31 (2)
	Zn	$M + L \rightleftharpoons ML$	4.31 (2)
		$M + 2L \rightleftharpoons ML_2$	8.42 (3)
		$M + L + H_2O \rightleftharpoons MLOH + H^+$	−1.07 (6)
		$M + 2L + H_2O \rightleftharpoons ML_2OH + H^+$	1.15 (9)
H_2O/CH_3OH 50%/50% *v/v*	Ni	$M + L \rightleftharpoons ML$	5.60 (5)
		$M + 2L \rightleftharpoons ML_2$	10.45 (6)
		$M + L + H^+ \rightleftharpoons MHL$	11.07 (3)
	Cu	$M + L \rightleftharpoons ML$	8.28 (6)
		$M + 2L \rightleftharpoons ML_2$	15.10 (8)
		$M + L + H^+ \rightleftharpoons MHL$	11.53 (4)
		$M + 2L + H_2O \rightleftharpoons ML_2OH + H^+$	2.32 (9)
	Zn	$M + L \rightleftharpoons ML$	4.87 (6)
		$M + 2L \rightleftharpoons ML_2$	9.06 (8)
		$M + 2L + H_2O \rightleftharpoons ML_2OH + H^+$	−1.95 (15)

Changes in the acid-base characteristics of ligands resulting from the change of solvent and the influence of substituents involving steric hindrances, clearly modify the complexing properties of the ligands. Table 2 presents the types of complex compounds and their stability constants in the system of *SARK* with Ni(II), Cu(II) and Zn(II) in water and water-methanol solution. Complex compounds with the remaining ligands have been discussed earlier[13–16]. Under the applied conditions nickel forms complexes of the type Ni*L* and NiL_2 in water; in water-methanol solution the presence of NiH*L* was also detected. In the case of copper the nature of equilibria is more complex. In both media, apart from the occurrence of Cu*L* and CuL_2 forms, the protonated compound CuH*L* was found. Furthermore, the compound Cu*L*OH is formed in water and CuL_2OH in mixed solvent. By analyzing the metal distribution among the particular types of complexes depending on *pH* (calculated with the aid of the HALTAFALL program[19]), information was obtained about the course of the chemical reactions (the problem was discussed more extensively in[13]). In the aqueous system, the compound Cu*L*OH is formed

as a result of an OH^- anion exchange for one ligand molecule, whereas the compound CuL_2OH (in mixed solvent) is formed by the addition of the anion to the CuL_2 complex. The complex $CuLOH$ is an intermediate between the CuL_2 complex and the hydroxide of the type $Cu(OH)_x$ precipitating at a high *pH*.

For all investigated cations, the stability of compounds was found to increase in mixed solvent (compared with water). This is due to a change of the basicity of functional groups as well as to differences in the solvation effect. A similar relationship is observed also for *DMG*, *N-PHEN* and *PHEN*. The stability of compounds with metals generally changes in the Zn < Ni < Cu series (in accordance with the *Irving-Williams* series) both in water and water-methanol solution. Comparing the complexes of both methyl derivatives of glycine (in the same medium) *SARK* complexes are more stable than those of *DMG*[13]. It can be assumed that the decrease in *DMG* stability is due to a lowered basicity of both functional groups and due to a change in steric conditions. By analyzing molecular models, one can notice that the spatial limitations concern primarily the metal-nitrogen bond.

However, when estimating the order of the stability constant changes for ML and ML_2 type complexes, a similar lowering in the K_1 and K_2 value was demonstrated either comparing the stability of *DMG* compounds in relation to *SARK* or *SARK* in relation to glycine[13]. This would suggest that the oxygen-metal bond is primarily responsible for the stability of complexes (the decrease in the K_2 value should be more pronounced than that in K_1 at an identical contribution of both coordinating functional groups, based on steric conditions). Thus the substitution of methyl groups at nitrogen changes the spatial arrangement to such a degree that the metal-nitrogen bond preferred in the case of transition metals under study is of less importance than the metal-oxygen bond. It should also be noted that the proton has a competitive role in relation to the metal cation and there are differences in the interaction of O—H and N—H. The above hypothesis is confirmed by ^{1}H-NMR studies. It was determined on the basis of methyl and methylene proton signal shifts that although both functional groups participate in the complexing process, the shift changes connected with $—CH_2$ protons neighbouring to the $—COO^-$ group are much clearer than those to the signals from the $—CH_3$ group protons[13]. The presented observations are in agreement with results which point to a higher complex stability in the system water-methanol. In the mixed solvent the basicity of the $—COO^-$ group increases, whereas that of the $—NH_2$ group diminishes. If the stability of the complex compounds is higher, it is the carboxylic group that must play a decisive role in bond formation (it must be kept in mind, however, that water and methanol molecules differ in solvation action). The role of the carboxylic group

manifests itself especially in zinc complexes with both phenyl derivatives of glycine. On the basis of ^{1}H-NMR and ^{13}C-NMR as well as IR[13,15,16] studies, it was found that only the carboxylic group participates in the coordination in these systems. Fig. 2 presents an example of ^{1}H-NMR signals changes due to complex formation in the *N-PHEN*/Zn system. The presence of Zn^{2+} has no influence on the band corresponding to the

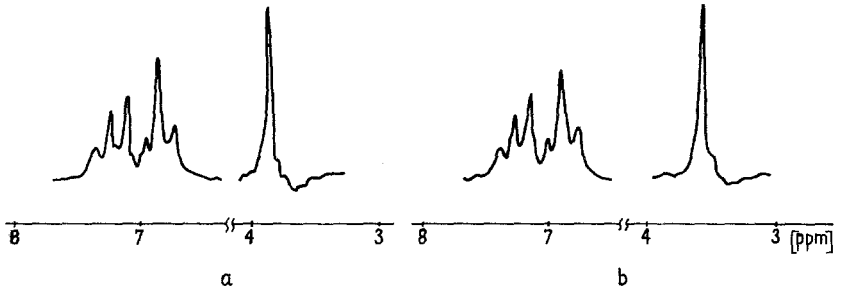

Fig. 2. ^{1}H-NMR spectra of *N*-phenylglycine (*a*), and of the *N*-phenylglycine/Zn system (*b*) in CD_3OD/D_2O 50%/50% *v/v*, *pD* = 5.5, $C_L = 0.05\,M$, $C_{Zn} = 0.025\,M$

phenyl protons (6.69–7.53 ppm). However, the singlet due to the —CH_2 protons is shifted from 3.90 to 3.57 ppm (in the case of nickel and copper complexes the both functional groups of *N-PHEN* take part in the coordination[13,15]. Infrared spectroscopic investigation points to a participation of —COO^- in the complexation (for example in 50%/50% *v/v* CD_3OD/D_2O solvent a shift in the asymmetric stretching vibration band from 1 618 cm^{-1} for *N-PHEN* to 1 602 cm^{-1} for *N-PHEN*/Zn is observed). The IR study suggests also[13,15] a symmetric structure of the carboxyl groups and a contribution of both oxygen atoms to the complex formation. Since Zn^{2+} contains a full (d^{10}) configuration, no crystal field effect occurs. Thus, the structure is determined mainly by electrostatic as well as covalent binding forces and by spatial conditions. Taking into consideration the above facts, a tetrahedral geometry (or at least close to it) is the most probable for *N-PHEN*/Zn complexes. A similar situation has been found in the case of *PHEN*/Zn complexes[13,16]. In these compounds, however, characteristic differences in *N-PHEN* and *PHEN* behaviour are seen. It was found[16] that the *PHEN*/Zn system in water gives rise to a protonated complex of the type $\overset{+}{N}H_3$—CH(*R*)—COO—Zn. The substitution of the phenyl group at nitrogen causes such a drop in the electron density on the nitrogen atom that the interaction between the proton and nitrogen becomes very slight. Consequently, despite the participation of only the carboxylic group of *N-PHEN* in the formation of

the compound, a protonated compound does not form, and only the complex $[NH(R)—CH_2—COO]_2Zn$ is formed under the analyzed conditions. Higher basicity of both functional groups of *PHEN* compared to those of *N-PHEN* as well as the change in steric conditions connected with the substitution of the phenyl group at the α carbon rather than at nitrogen, is the reason for the much higher stability of *PHEN* compounds compared to those of *N-PHEN*[15,16].

Table 3. *Protonation constants of MHL and M(HL)L complexes in water and in water-methanol solvent (50%/50% v/v)*

Ligand	Reaction	Solvent	$\log K^{H}$
SARK	$CuL + H^+ \rightleftharpoons CuHL$	H_2O	3.66
SARK	$CuL + H^+ \rightleftharpoons CuHL$	CH_3OH/H_2O	3.25
DMG	$CuL_2 + H^+ \rightleftharpoons Cu(HL)L$	H_2O	4.87
DMG	$CuL_2 + H^+ \rightleftharpoons Cu(HL)L$	CH_3OH/H_2O	4.55
SARK	$NiL + H^+ \rightleftharpoons NiHL$	CH_3OH/H_2O	5.47
DMG	$NiL + H^+ \rightleftharpoons NiHL$	CH_3OH/H_2O	5.84
PHEN	$ZnL + H^+ \rightleftharpoons ZnHL$	H_2O	6.92

$$K^{H}_{MHL} = \frac{[MHL]}{[ML][H^+]}, \quad K^{H}_{M(HL)L} = \frac{[M(HL)L]}{[ML_2][H^+]}.$$

The dependence of the equilibrium constant K of the formation of protonated sarcosine compounds ($M + HL \rightleftharpoons MHL$) on the basicity of the carboxylic group was established. The amino group of this type compound is blocked by a proton, and only the $—COO^-$ group takes part in the coordination. *Childs* and *Perrin* determined earlier[21]: $\log K = 1.53$ for the system of glycine/Cu in water. It was found in the present study that in the *SARK*/Cu system in water $\log K = 1.44$.

This value is lower than for glycine-containing system, the basicity of the $—COO^-$ group being also lower (the pK_1 values for glycine and sarcosine are 2.40 and 2.22, respectively). In the *SARK*/Cu system in water-methanol solution 50%/50% *v/v*, $\log K = 1.76$, which is in agreement with the higher basicity of the carboxylic group (pK_1 of *SARK* in mixed solvent is 2.82). It is also a characteristic phenomenon that for all protonated complexes found in the analyzed systems, the increase in metal-ligand bond stability (as reflected by the stability constant of *ML* type complexes) causes a weakening of the nitrogen-proton bond (Table 3 presents the protonation constants K^H of the complexes studied). This can be explained by a decrease in the electron density on nitrogen as a result of

the presence of an electron-accepting metal cation and of an electrostatic interaction of this cation with the proton. The above conclusions apply both to changes in the metal-ligand interaction resulting from a solvent change and to modifications of complexing properties of the ligand due to differences in the amino acid structure.

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