

Estimation of Stability Constants of Copper(II) Chelates with *N*-alkylated Amino Acids using Topological Indices

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Received April 16, 1999; revised July 9, 1999; accepted July 22, 1999

Protonation (pK_1 and pK_2) and copper(II) binding stability constants ($\log \beta_{110}$ and $\log \beta_{120}$) of glycine and five *N*-alkylated glycines (methyl, dimethyl, diethyl, *tert*-butyl and *tert*-butylmethyl) were determined by potentiometric titration. These constants and the constants of eight *N*-alkylated glycines, measured previously, were correlated with four topological indices (Wiener index, W , and the first-, second- and third-order valence-connectivity indices, ${}^1\chi^v$, ${}^2\chi^v$ and ${}^3\chi^v$) calculated for the ligand.

The first protonation constants (ascribed to the dissociation of COOH group) do not correlate with any of the chosen topological indices ($r^2 < 0.3$), but significant correlation was obtained for pK_2 (dissociation of amino group) with r^2 values up to 0.920. »Corrected« stability constants (obtained by subtracting pK_2 value) yielded a generally better fit than the uncorrected ones. Our stability constants are better correlated with topological indices (max. $r^2 = 0.993$) than the constants measured previously (max. $r^2 = 0.836$). From the regression analysis it is possible to predict the values of pK_2 , $\log \beta_{110}$ and $\log \beta_{120}$ with an error less than 0.1, 0.3 and 0.3 log units, respectively.

Key words: Stability constants, Copper(II) chelates, *N*-alkylated glycines, topological indices

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INTRODUCTION

Copper(II) chelates with *N*-alkylated and *N,N*-dialkylated amino acids¹ are very suitable model compounds for studies of sterical interactions in the class of copper(II) complexes with amino acids and similar biologically interesting compounds (Figure 1).

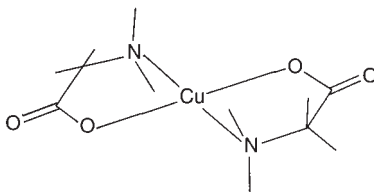


Figure 1. General structure formula of copper(II)bis-complexes with glycine and its *N*-alkylated derivatives.

Enantioselectivity effect observed in this class of compounds,^{2,3} was not observed in the complexes with naturally occurring amino acids.⁴ Also, complexes of *N*-alkylated amino acids with copper(II) show a very pronounced distortion of coordination polyhedron,⁵⁻⁷ this has made them suitable for development of molecular mechanics models for complexes with flexible geometry.⁸⁻¹¹ Recently, a new method for estimation of conformational energy (sterical interactions among chelate rings) based on the model of overlapping spheres was checked on this class of compounds.¹²

Molecular mechanics calculations showed that the stability of copper(II) chelates (*i.e.* enantioselectivity effect) with *N*-alkylated amino acids in aprotic solutions was dependent on sterical interactions among the bulky groups of ligands.^{13,14} However, the estimation of stability constants of topologically different molecules is not an easy task for molecular mechanics, and other sophisticated methods (*e.g.* methods based on continuous distributions of solvents^{15,16} and molecular dynamics¹⁷).

The aim of this paper is to use topological indices of ligands in the structure-stability constants modeling for copper(II) chelates with *N*-alkylated and *N,N*-dialkylated amino acids and to compare the models developed from two sets of stability constants for *N*-alkylated and *N,N*-dialkylated glycines (old set¹⁸ and the set from this paper).

EXPERIMENTAL

Materials and Methods

The ligands, *N,N*-dimethyl- and *N,N*-diethylglycine, were prepared by condensation of glycine with the corresponding aldehydes, *i.e.* formaldehyde and acetaldehyde.

de. The catalytic hydrogenation was carried out over three days at room temperature and 1.5 bar in ethanol/water (1:1) solution.¹⁹

After removing the catalyst, the products were recrystallized from ethanol/ether solution giving *N,N*-dimethylglycine (m.p. 178–180 °C) and *N,N*-diethylglycine (m.p. 131–132 °C). *N-tert*-butylglycine (m.p. 201–202 °C, total yield 33%) was prepared according the known procedure.²⁰ This product was condensed with formaldehyde, followed by catalytic hydrogenation, as described before, and recrystallized from ethanol (total yield 30%).

Protonation and stability constants were determined at 25 °C in aqueous KNO₃ (0.1 mole L⁻¹) solution by potentiometric titration. Acidified solution (HNO₃) of ligands (10 mL *ca* 0.005 mol L⁻¹) in a thermostated double walled glass vessel was titrated with aqueous KOH (0.06 mol L⁻¹) with the same background electrolyte. Purified argon was bubbled through the solution during titration. For the determination of stability constants, an adequate amount of Cu²⁺ (2.5 to 5.0 mL of 0.005 mol L⁻¹ Cu(NO₃)₂) was used.

The measuring system was calibrated in terms of hydrogen concentration according to Irving's recommendations.²¹ The apparatus was standardized on the conventional pH scale²² by measuring the e.m.f. in two buffer solutions (potassium hydrogenphthalate and borax) and by calibration titration of HNO₃ in background electrolyte before and after each experiment.

Potentiometric titrations were performed by means of a Metrohn titrator 736 GP Titrino equipped with a combined glass electrode and Metrohn TiNet-2.1 software connection. The initial estimates of the protonation and stability constants were refined using the SUPERQUAD program.²³

DEFINITIONS OF THE TOPOLOGICAL INDICES

The chemical graph theory^{24,25} provides a number of topological indices,^{26–28} but only a few of them have been used in QSPR (quantitative structure-properties relationships) studies^{29–35} (*e.g.* the Wiener index, the connectivity index, and the connectivity index extended to heteroatoms). The indices are computed from the hydrogen-suppressed molecular structures.^{36,37} In this paper, we used the following topological indices:

(a) *The Wiener index*,^{38–40} $W(G) = W$, of a structure G is calculated from the distance matrix \mathbf{D} of the corresponding hydrogen-suppressed chemical graph G .^{41,42}

$$W = (1/2) \sum_{i,j} (D)_{ij} \quad (1)$$

where $(D)_{ij}$ represents the off-diagonal elements of \mathbf{D} . It is the shortest distance (*i.e.* path) in terms of the number of bonds between atoms i and j in G . Distance $i-j$ has to be weighted in the case of heterosystems,^{39,43} as in our case.

(b) *The Vertex-Connectivity Index*, $\chi = \chi(G)$, of a (molecular) graph G is defined as:⁴⁴

$$\chi = \sum_{\text{edges}} [d(v_i) d(v_j)]^{-1/2}. \quad (2)$$

The sum is taken over all edges of G ; $d(v_i)$ is the vertex-degree and $[d(v_i) d(v_j)]^{-1/2}$ is the weight of the i - j edge. The degree of a vertex v_i , $d(v_i)$, is equal to the number of adjacent vertices. Two vertices of graph G are adjacent if there is an edge joining them.

In the case of heterosystems, the connectivity index is given in terms of valence delta values $\delta(v_i)$ and $\delta(v_j)$ of atoms i and j . This kind of connectivity index (valence-connectivity index, χ^v) is defined as:²⁹

$$\chi^v = \sum_{i,j} [\delta(v_i) \delta(v_j)]^{-1/2}. \quad (3)$$

Valence delta values are available for many kinds of atoms.^{29,33,36} The connectivity index can be generalized to include also the weighted paths p_e of length l , not only the weighted edges (weighted path p_l of length one):⁴⁵⁻⁴⁷

$${}^l\chi = \sum_{\text{paths}} [d(v_i) d(v_j) \dots d(v_{l+1})]^{-1/2} \quad (4)$$

where $d(v_i)$, $d(v_j)$, ..., $d(v_{l+1})$ are valences of vertices v_i , v_j , ..., v_{l+1} in the considered path of length l . The first-, ${}^1\chi^v$, second-, ${}^2\chi^v$, and third-order, ${}^3\chi^v$, valence-connectivity indices in this paper are calculated by Eq. (4) when valence delta values are introduced into it for heterosystems.

RESULTS AND DISCUSSION

The non-empirical structure-property relationships for the protonation and stability constants of the copper(II) chelates with N -alkylated and N,N -dialkylated glycine using experimental values by Basolo and Chen (Table I)¹⁸ were established. However, we also repeated measurements of constants pK_1 , pK_2 , $\log \beta_{110}$ and $\log \beta_{120}$ for the chelates studied by Basolo and Chen, including two additional structures (Table I).

The objective was to compare the structure-property model based on previous measurements¹⁸ and the model based on our measurements.

Non-empirical structure-property relationships are based on topological indices.^{34,37,43,44} The topological indices used in this paper are the Wiener index (W), the first-order, (${}^1\chi^v$), the second-order (${}^2\chi^v$) and the third-order (${}^3\chi^v$) valence-connectivity index. These indices of the ligands are presented in Table II.

TABLE I

Stability constants of copper chelates with *N*-alkylated and *N,N*-dialkylated amino acids (Ref. a = our paper*; Ref. b = Ref. 18)

Ligand	p <i>K</i> ₁		p <i>K</i> ₂		log β ₁₁₀ **		log β ₁₂₀ **	
	a	b	a	b	a	b	a	b
Gly	2.378(8)	2.43	9.667(4)	9.62	8.270(11)	8.38	15.233(10)	15.17
MeGly	2.174(2)	2.24	10.007(3)	10.01	7.740(1)	7.94	14.276(12)	14.59
Me ₂ Gly	1.879(7)	2.08	9.788(6)	9.80	7.276(3)	7.30	13.902(8)	13.65
EtGly		2.30		10.10		7.34		13.55
Et2Gly	1.842(10)	2.04	10.429(3)	10.47	6.848(2)	6.88	13.383(25)	12.86
<i>n</i> -PrGly		2.28		10.03		7.25		13.31
<i>n</i> -BuGly		2.29		10.07		7.32		13.52
ButGly	2.292(6)		10.202(17)		6.059(18) 6.096(15)** 6.303(15)		12.177(13)	
MeButGly	1.940(28)		10.646(17)		6.730(3)			
<i>i</i> -PrGly		2.36		10.06		6.70		12.45

* *I* = 0.1 mol dm⁻¹ (KNO₃), *T* = 298.15 K; standard error is given in the parentheses.

** Stability constants are defined according to the formula:

$$\beta_{klm} = [\text{M}_k \text{L}_l \text{H}_m] / [\text{M}]^k [\text{L}]^l$$

*** Assuming log β₁₁₋₁ = -0.561(30)

TABLE II

Four topological indices for ligands: the Wiener index (*W*), and the first-, second- and third-order valence-connectivity indices (¹χ^v, ²χ^v and ³χ^v)

Ligand	<i>W</i>	¹ χ ^v	² χ ^v	³ χ ^v
Gly	14	1.1701	0.5761	0.1667
MeGly	26	1.6154	0.9023	0.3211
Me2Gly	40	1.9725	1.6098	0.4453
Et2Gly	84	3.1247	1.8334	1.2471
ButGly	86	2.8654	2.9756	0.7631
MeButGly	107	3.2488	3.3989	1.5114
EtGly	44	2.1760	1.1523	0.5193
<i>n</i> -PrGly	69	2.6760	1.5488	0.6961
<i>n</i> -BuGly	102	3.1760	1.9023	0.9764
<i>i</i> -PrGly	64	3.3765	1.9076	0.6547

TABLE III

Linear regression of stability constants on topological indices; N , the number of ligands; r^2 , the correlation coefficient; RMS , the root-mean-square residual; F , the Fisher ratio; Ref. a = our paper; Ref. b = Ref. 18

Index	N	r^2	Slope	Intercept	RMS	F	Ref.
Independent variable: pK_2							
${}^3\chi^v$	6	0.920	0.671	9.625	0.119	46.144	a
${}^3\chi^v$	8	0.735	0.599	9.643	0.136	16.632	b
Independent variable: $\log \beta_{110}$ (Bu ^t Gly, $\log \beta_{110} = 6.059$)							
W	6	0.764	-0.018	8.234	0.426	12.933	a
${}^2\chi^v$	6	0.789	-0.624	8.328	0.403	14.930	a
${}^2\chi^v$	8	0.836	-0.954	8.740	0.237	30.495	b
Independent variable: $\log \beta_{110}$ (Bu ^t Gly, $\log \beta_{110} = 6.303$)							
W	6	0.818	-0.017	8.221	0.343	18.014	a
${}^1\chi^v$	6	0.834	-0.761	8.967	0.328	20.132	a
${}^2\chi^v$	8	0.836	-0.954	8.740	0.237	30.495	b
Independent variable: $\log \beta_{120}$							
${}^2\chi^v$	5	0.961	-1.186	15.668	0.258	73.697	a
${}^2\chi^v$	8	0.808	-1.582	15.898	0.415	25.316	b
Independent variable: $\log \beta_{110} - pK_2$ (Bu ^t Gly, $\log \beta_{110} = 6.059$)							
W	6	0.916	-0.027	-1.342	0.349	43.707	a
${}^1\chi^v$	6	0.917	-1.194	-0.184	0.347	44.454	a
${}^1\chi^v$	8	0.812	-0.823	-0.647	0.344	25.858	b
Independent variable: $\log \beta_{110} - pK_2$ (Bu ^t Gly, $\log \beta_{110} = 6.303$)							
W	6	0.941	-0.026	-1.355	0.280	63.750	a
${}^1\chi^v$	6	0.950	-1.159	-0.224	0.257	76.485	a
${}^1\chi^v$	8	0.812	-0.823	-0.647	0.344	25.858	b
Independent variable: $\log \beta_{120} - 2pK_2$ (Bu ^t Gly, $\log \beta_{110} = 6.059$)							
W	6	0.923	-0.047	-3.890	0.523	35.875	a
${}^1\chi^v$	8	0.829	-1.436	-2.940	0.566	29.073	b
Independent variable: $\log \beta_{110} - \log \beta_{120} - pK_2$ (Bu ^t Gly, $\log \beta_{110} = 6.059$)							
W	6	0.993	-0.025	-8.095	0.078	445.640	a
${}^1\chi^v$	6	0.985	-7.218	-0.184	0.165	97.647	a
${}^3\chi^v$	8	0.729	-0.992	-8.267	0.229	16.178	b

Stability constants (Table I) decrease with the size of the substituent(s). This tendency was pointed out in the earlier paper¹⁸ and was tentatively ascribed to the destabilization of a complex due to steric hindrance. The same decreasing trend is also obvious for the second protonation constant (pK_2), but it is hard to make any generalization for the first protonation constant (pK_1). For the *N*-methyl-*N*-*tert*-butylglycine system, the stability constant for bis-complex could not be obtained, and *N*-*tert*-butylglycine gave three solutions upon refinement. If in the latter case only formation of mono-complex was proposed, iterative procedure yielded $\log \beta_{110} = 6.303(15)$. If the formation of bis-complex and deprotonation of mono-complex was assumed, $\log \beta_{110}$ values of 6.059(18) and 6.096(15) were obtained, respectively.

Four topological indices yielded consistent results, obtained by regression analysis, (Table III). Parameters for linear regression of the stability constants (pK_2 , $\log \beta_{110}$, $\log \beta_{110} - pK_2$, $\log \beta_{120} - 2pK_2$, $\log \beta_{110} - \log \beta_{120} - pK_2$) on topological indices are shown in Table III for both sets of ligands, our (set *a*) and the one from the literature (set *b*).¹⁸

Regression analysis gives for both sets (*a* and *b*) with all topological indices the same slope direction (Figure 2 and Figure 3).

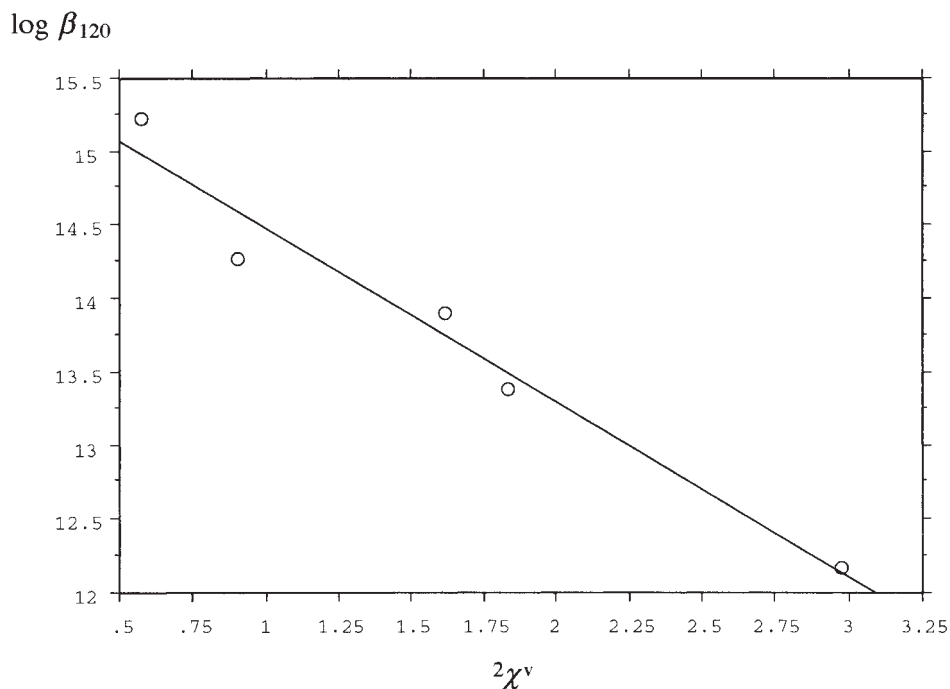


Figure 2. Linear regression of our $\log \beta_{120}$ on $2\chi^v$ ($\log \beta_{120} = -1.186 2\chi^v + 15.668$, see Table III).

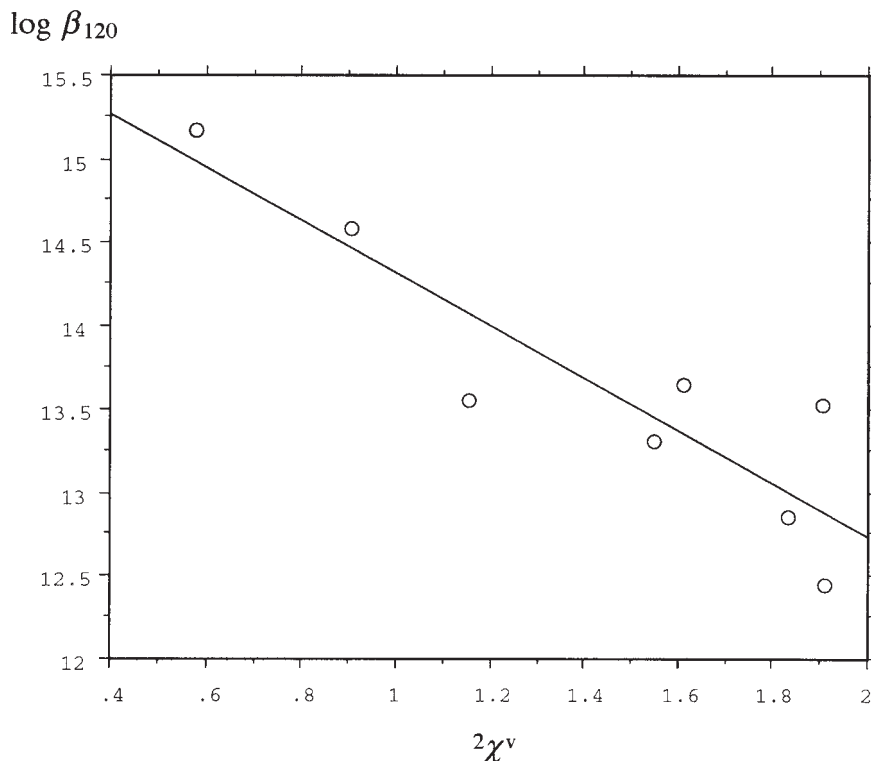


Figure 3. Linear regression of previously measured¹⁸ $\log \beta_{120}$ on $2\chi^v$ ($\log \beta_{120} = -1.582 \cdot 2\chi^v + 15.898$, see Table III).

Generally, the first and the second stability constants are equally well correlated on topological indices. r^2 values in Table III clearly show that our set of constants is generally better correlated than the set of constants measured previously. In Table III, we also give the values of the root-mean-square residual, *RMS*, or standard error of estimate with $N-i-1$ in denominator, where i is the number of descriptors involved in the model. The disagreement is mainly due to the fact that stability constants do not drastically change with the length of aliphatic chain ($\log \beta_{110}$ is 7.34, 7.25 and 7.32 for ethyl, *n*-propyl and *n*-butyl derivative, respectively, Table I).¹⁸ Contrary to pK_2 , the first protonation constant (pK_1) is uncorrelated with topological indices ($r^2 < 0.3$). (pK_1 is ascribed to deprotonation of carboxylic group, and therefore it is least influenced by the substituents on nitrogen atom.)

Better correlations for both sets of data were obtained if the pK_2 value was subtracted from stability constants. This is to be expected because the

TABLE IV
 Estimation of stability constants from linear regression analysis

Amino acid	pK_2^a	$\log \beta_{110}^b$	$\log \beta_{110}^c$	$\log \beta_{120}^d$
Gly	9.737	8.078	8.087	14.985
MeGly	9.840	7.739	7.911	14.598
Me ₂ Gly	9.924	7.468	7.278	13.759
Et ₂ Gly	10.462	6.592	6.583	13.494
Bu ^t Gly	10.137	6.789	6.657	12.139
MeBu ^t Gly	10.639	6.498	6.657	11.637

$$^a pK_2 = 0.671 \chi^v + 9.625$$

$$^b \log \beta_{110} = -0.761 \chi^v + 8.967$$

$$^c \log \beta_{110} = -1.159 \chi^v - 0.224 + pK_2$$

$$^d \log \beta_{120} = -1.186 \chi^v + 15.668$$

subtraction of pK_2 should be viewed as some kind of correction for electronic effects. The results obtained for the linear regression with the best r^2 fit are presented in Table IV.

Stability constants were reproduced with an error less than 0.4 on the log scale (0 – 0.1 for pK_2 , 0 – 0.3 for $\log \beta_{110}$, and 0.1 – 0.3 for $\log \beta_{120}$). The decreasing order of stability constants was also correctly reproduced. The data in Table III show that the valence-connectivity indices (χ^v) gave the best fit and also the smallest difference between the r^2 for a and b set. Nevertheless, the differences are not critical to exclude the use of other indices.

In conclusion, it can be stated that stability constants are reasonably well correlated with topological indices. Therefore, the use of QSPR with topological indices should be recommended as an initial step in studies of the stability of complex compounds.

Acknowledgments. – This work was supported by the Ministry of Science and Technology of the Republic of Croatia through grants no. 00980606 and 00220101. Our thanks are also due to Professors Vladimir Simeon and Nikola Kallay for their help in determining stability constants.

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SAŽETAK

Procjena konstanti stabilnosti kelata bakra(II) s *N*-alkiliranim aminokiselinama uporabom topologijskih indeksa

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Protonacijske konstante (pK_1 , pK_2) i konstante stabilnosti ($\log \beta_{110}$ i $\log \beta_{120}$) za komplekse bakra(II) s *N*-alkiliranim glicinima (metil, dimetil, dietil, *tert*-butil i *tert*-butilmetil) određene su potenciometrijskom titracijom. Te konstante i konstante za osam *N*-alkiliranih glicina, koje su prije određene, korelirane su sa četiri topologijska indeksa (Wienerov indeks, W , te indeksi valencijske povezanosti prvog, drugog i trećeg reda, ${}^1\chi^v$, ${}^2\chi^v$ i ${}^3\chi^v$). Ti su indeksi izračunani iz strukturne formule liganda.

Prva konstanta protonacije (pripisana disocijaciji karboksilne skupine) nije korelirana ni s jednim od navedenih topologijskih indeksa ($r^2 < 0,3$), no značajna je korelacija dobivena za pK_2 (disocijacija amino-skupine) s maksimalnom vrijednošću $r^2 = 0,920$. "Korigirane" konstante stabilnosti (dobivene oduzimanjem vrijednosti pK_2) općenito daju bolje slaganje od nekorigiranih konstanti. Naše konstante stabilnosti bolje su korelirane s topologijskim indeksima (max. $r^2 = 0,993$) od prije izmjerenih konstanti stabilnosti (max. $r^2 = 0,836$). Iz regresijske analize moguće je predvidjeti vrijednosti konstanta s pogreškom manjom od 0,1 (pK_2) i 0,3 ($\log \beta_{110}$, $\log \beta_{120}$).