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Estimation of Stablity Constants of Mixed Amino Acid Complexes with Copper(II) from Topological Indices*,#

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Stability constants of binary and ternary complexes of five naturally occurring amino acids (Gly, Ala, Val, Phe, Tyr) with copper(II) were correlated with the Wiener (W) and the valence-connectivity indices (χ) of their ML_2 complexes, yielding the correlation coefficient r = 0.931–0.997 and the root-mean-square (rms) deviation of the measured and estimated values in the range of 0.013 to 0.065 log K units. Multiple regression of 27 second ligation constants of binary and ternary complexes of 10 amino acids (Gly, Ala, Val, Leu, Ser, Thr, Met, Phe, Tyr, Trp) on topological indices of various molecular species (L, ML, ML_2) yielded R = 0.696–0.756 and rms = 0.17–0.19 log K_2 units. The result is essentially better than the results obtained by the mechanistic method of M. Tabata and M. Tanaka (see Ref. 8) on the same set of data (rms = 0.39 log K_2 units). The method appeared to be sensitive to the amino acid ability of additional (apical) coordination, but not very sensitive to other structural properties (aromaticity, polarity). Among the models used, the best results were obtained with the third-order valence-connectivity index ($^3\chi^v$) calculated from the formula of complex compounds (ML and ML_2).

Key words: stability constants, copper(II) chelates, topological indices.

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* Dedicated to Professor Smiljko Ašperger on the occasion of his 80th birthday.

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INTRODUCTION

Estimation of the stability constants of coordination compounds is not an easy task because their stability is determined by many, often unrelated, factors: electronic (strength of the metal-ligand bond), stereochemical (mode of coordination), steric hidrance among bulky groups, energy of solvation (hydration) for the metal, ligand and the complex, *etc*. It is, therefore, virtually impossible to develop a method that could deal with all these heterogeneous influences. Simple empirical rules (Irving-Williams order,[1] A-, B-, C-metal,[2] (a)- and (b)- cation[3] classification, along with the distinction of »hard« and »soft« (Lewis) acids and bases (HSAB)[4,5]) were followed by more sophisticated quantitative models. These models are based on the »interaction parameters« between atoms in the first coordination sphere,[6–8] or on the difference in steric strain (conformational energy), which is evaluated by the molecular mechanics method.[9–14] Recently, methods based on continuous distribution of solvents[15,16] and molecular dynamics[17] have been used to estimate the stability of coordination compounds.

Due to computational simplicity, correlations of topological indices would provide an easy method for the estimation of stability constants. Moreover, the success of the approach might arise from the fact that topological indices unite diverse properties of a molecule; topological indices were found to be successfully correlated with physicochemical parameters (density, viscosity, boiling temperature, solubility, refractive index, molar heat capacity, standard Gibbs energy of formation),[18–21] chromatography-related properties (adsorptivity),[22] and biological activity.[23–27]

In our first paper on the application of topological indices for estimation of the stability of coordination compounds,[28] we used the Wiener index (W) and the first three valence-connectivity indices ($^1\chi^v$, $^2\chi^v$, $^3\chi^v$) to estimate the protonation and copper-binding constants for ten *N*-alkylated glycinates. (Complexes of *N*-alkylated amino acids[29] are interesting primarily because of stereochemical effects).[30,31] Using linear regression we succeeded in estimating the stability constants with the error of 0.01 to 0.32 on the log scale. In this paper we are primarily concerned with further development of our approach. The first improvement is the calculation of topological indices for mono- and bis-complexes, which enabled us to deal with mixed complexes, and the second improvement is the use of the multiple regression method for the estimation of stability constants from topological indices.

METHODS

The chemical graph theory[32,33] provides a number of topological indices. Topological index is a molecular descriptor, which is the final result of a logical and mathematical procedure that transforms chemical information

encoded within the symbolic graph representation of a molecular structure into a useful number.[34]

The Wiener index,[35] $W(G) = W$, of a structure (graph) G is defined[36] as the half-sum of the off-diagonal elements of the molecular distance matrix[37] $\boldsymbol{D}$ of the corresponding hydrogen-suppressed chemical graph G:

$$W = (1/2) \sum_i \sum_j (D)_{ij} \tag{1}$$

where $(D)_{ij}$ represents the off-diagonal elements of $\boldsymbol{D}$. It is the shortest distance (*i.e.* path) in terms of the number of bonds between atoms i and j in G. There are also other formulations of the Wiener index in the literature.[32,34,38]

The valence-connectivity index,[24,33,39,40] $\chi(G) = \chi$, of a molecular graph G with heteroatoms is defined as:

$$\chi^{v} = \sum_{ij} (\delta_i \, \delta_j)^{-1/2} \tag{2}$$

where δ_i and δ_j are valence delta values of adjacent atoms i and j forming a bond, other than hydrogen. The summation runs over the non-hydrogen atoms of the entire molecule. The valence-connectivity indices of different order are defined as:[24,32]

$$^{\ell}\chi^{v} = \sum (\delta_i \, \delta_j \ldots \delta_{\ell+1})^{-1/2} \tag{3}$$

where $\delta_i \, \delta_j \ldots \delta_{\ell+1}$ are weights (valence-delta values) of vertices (atoms) *i, j,…*, ℓ+1 making up the path of length ℓ in a vertex-weighted molecular graph.

Valence delta values are available for many kinds of atoms.[41,42] The valence delta value for copper atoms in molecules of complex compounds is δ_{Cu} = 0.647 and was calculated from the formula:[24,32,41,42]

$$\delta_i = (Z_i^{v}) / (Z_i - Z_i^{v} - 1) \tag{4}$$

where Z_i^{v} is the number of valence electrons and Z_i is the atomic number of the corresponding atom i. In the case of a copper atom, the values are Z_i = 29, and Z_i^{v} = 11.

The sum-delta molecular connectivity index,[43] $D(G) = D$, of a molecular graph G with heteroatoms is defined as:

$$D = \sum_i \delta_i \tag{5}$$

where the summation runs over the vertices (atoms) of the chemical graph including only the nonhydrogen atoms of the molecule. In our work, the D values for ten amino acids were taken from the literature.[44]

The values of topological indices for copper(II) chelates are presented in Table I.

TABLE I

Topological indices of ML and ML_2 complexes (δ_{Cu} = 0.647)[a]

Complex	W	$^1\chi^v$	$^2\chi^v$	$^3\chi^v$
CuGly	31	2.3954	1.6305	1.0527
CuAla	46	2.8329	2.0689	1.5592
CuSer	68	2.9525	2.0534	1.5484
CuVal	92	3.7436	3.0500	2.0027
CuThr	92	3.4020	2.5112	1.7902
CuLeu	130	4.2268	3.5163	2.0941
CuPhe	308	4.9281	3.5765	2.6672
CuTyr	384	5.0623	3.7573	2.7608
CuTrp	518	5.9291	4.4504	3.4835
CuMet	137	3.8607	2.6682	2.0018
$Cu(Gly)_2$	162	4.7907	4.4686	3.6151
$Cu(Ala)_2$	248	5.6658	5.3455	4.4355
$Cu(Ser)_2$	374	5.9050	5.3145	4.4138
$Cu(Val)_2$	520	7.4872	7.3078	5.3225
$Cu(Thr)_2$	520	6.8039	6.2230	4.8974
$Cu(Leu)_2$	746	8.4535	8.2402	5.5054
$Cu(Phe)_2$	1816	9.8561	8.3606	6.6516
$Cu(Tyr)_2$	2302	10.1247	8.7223	6.8386
$Cu(Trp)_2$	3226	11.8441	10.1084	8.2842
$Cu(Met)_2$	778	7.7215	6.5441	5.3207
Cu(Gly)(Ala)	202	5.2283	4.9071	4.0253
Cu(Gly)(Ser)	254	5.3754	4.9075	4.0316
Cu(Gly)(Thr)	308	5.8198	5.3848	4.2703
Cu(Gly)(Tyr)	840	7.4577	6.5955	5.2269
Cu(Gly)(Phe)	709	7.3234	6.4146	5.1333
Cu(Ala)(Ser)	307	5.8130	5.3459	4.4418
Cu(Ala)(Thr)	368	6.2574	5.8232	4.6805
Cu(Ala)(Tyr)	953	7.8953	7.0339	5.6371
Cu(Ala)(Phe)	810	7.7610	6.8531	5.5436
Cu(Val)(Tyr)	1221	8.8060	8.0150	6.0805
Cu(Ser)(Thr)	443	6.4045	5.8236	4.6868
Cu(Ser)(Tyr)	1086	8.0424	7.0343	5.6434
Cu(Ser)(Phe)	930	7.9081	6.8534	5.5498
Cu(Thr)(Tyr)	1221	8.4868	7.5116	5.8820
Cu(Thr)(Phe)	1052	8.3525	7.3308	5.7885
Cu(Tyr)(Phe)	2050	9.9904	8.5414	6.7451
Cu(Tyr)(Trp)	2736	10.9844	9.4153	7.5614

[a] δ_{Cu}, the valence delta value for copper atom (Eq. 4); W, the Wiener index; χ, the valence-connectivity indices.

RESULTS AND DISCUSSION

For the estimation of stability constants of bis-complexes (log β_{12}) we chose five binary and six ternary copper(II) complexes with naturally occurring amino acids which are incapable of additional (apical) coordination and were measured under the same conditions (25 °C, I = 0.05 mol L^{-1} (KNO_3).[45] Linear regression on four topological indices of bis-complexes gave excellent agreement with the experiment (Table II).

TABLE II

Linear regression of log β_{120} on the topological indices of ML_2 (or MAL) complexes[a,b]

No.	N	Index	Slope	Intercept	$\lvert r \rvert$	rms
1	5	$^1\chi^v$	–0.063 (0.006)	15.384(0.045)	0.988	0.027
2	11	$^1\chi^v$	–0.062 (0.005)	15.395(0.043)	0.967	0.032
3	5	$^1\chi^v$	–0.081 (0.009)	15.457(0.065)	0.981	0.035
4	11	$^2\chi^v$	–0.080 (0.007)	15.469(0.046)	0.970	0.030
5	5	$^3\chi^v$	–0.110 (0.005)	15.496(0.026)	0.997	0.013
6	11	$^3\chi^v$	–0.108 (0.008)	15.504(0.046)	0.973	0.029
7	5	W	$-1.459(0.33) \cdot 10^{-4}$	15.051(0.044)	0.931	0.065
8	11	W	$-1.485(0.17) \cdot 10^{-4}$	15.068(0.021)	0.943	0.042

[a] r, the correlation coefficient; rms, the root-mean-square deviation of residuals.

[b] Regressions with N = 5 and N = 11 correspond to binary and binary plus ternary complexes, respectively. Stability constants correspond to complexes 1, 2, 4, 7, 8, 11, 14, 15, 18, 19, 20 and 26, as denoted in Figure 2. All stability constants (β_{120} = [MAL] $[M]^{-1}$ $[A]^{-1}$ $[L]^{-1}$) were measured at I = 0.05 mol L^{-1}, T = 25 °C. The constants of mixed complexes were corrected for statistical factor (log β_{120}(corr) = log β_{120} – log 2).[8]

Regression coefficients of all regressions are higher than 0.93 (r = 0.931–0.997), and agreement between the measured and calculated data, expressed as the root-mean-square deviation of residuals, is in the range of 0.01 to 0.07. In the best regression (no. 5, Table II), the maximum residual value is 0.02 (for $CuAla_2$), and the minimal value is 0.00 (for $CuVal_2$ and $CuTyr_2$). All values of the first regression coefficients (slope) are < 0, as obtained by similar calculations on N-alkylated glycinates.[28] The values of slopes and intercepts were not significantly changed after addition of six mixed complexes to the set. There are no great differences between the estimated values obtained by different topological indices, but the third-order valence connectivity index ($^3\chi^v$) appears to be most promising (Figure 1). This finding is in agreement with the conclusion of our previous paper.[28]

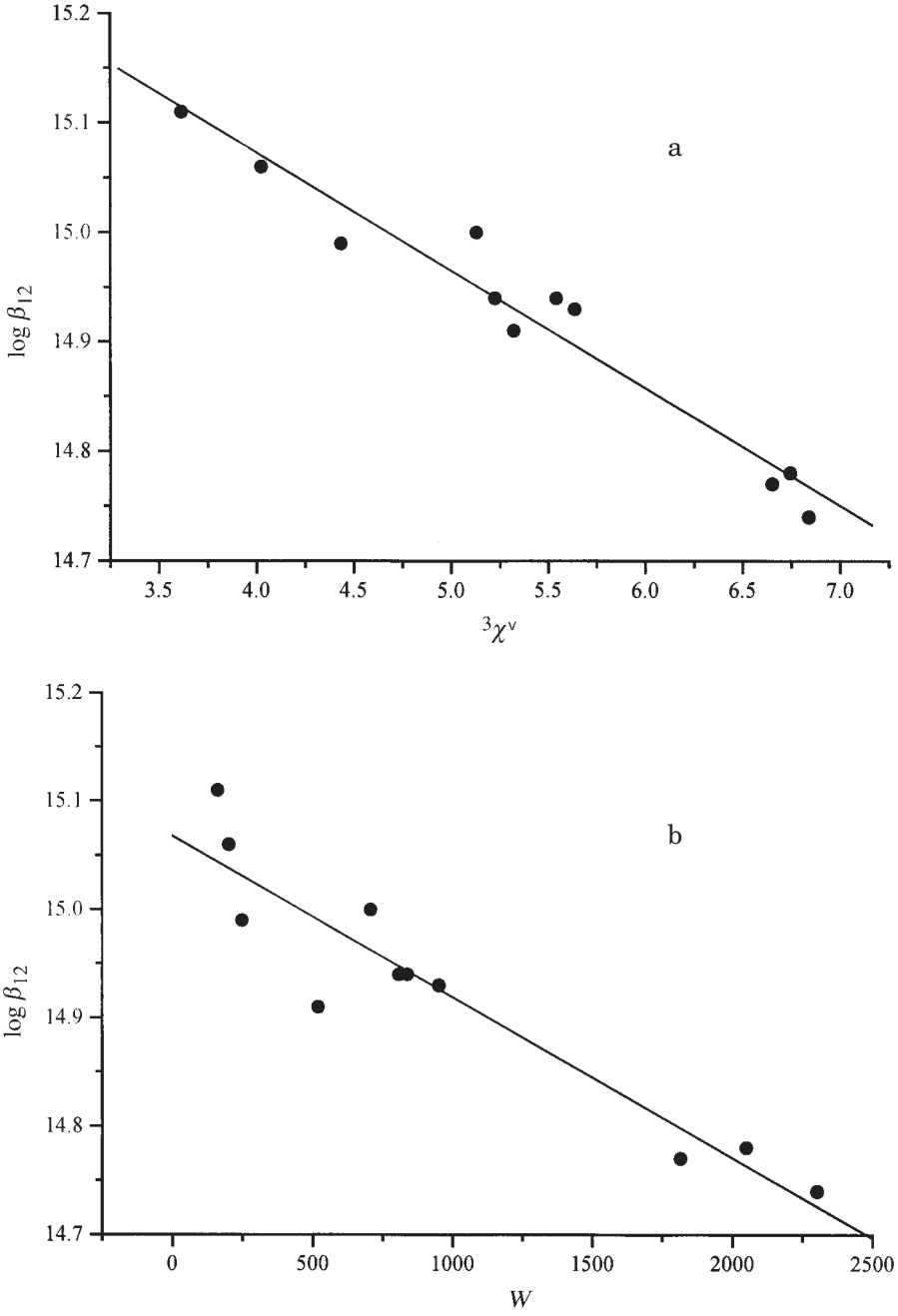

Figure 1. (a) Linear regression of $\log \beta_{12}$ values for five binary and six ternary complexes on the third-order valence-connectivity index, $^3\chi^v$, (regr. 6, Table II) and (b) Wiener index, W, (regr. 8, Table II), as calculated for the graph of ML_2 complexes.

Selection of stability constants is essential. The difference between the calculated (regr. 1) and measured values at different ionic strength (I = 0.1 mol L^{-1}) is 0.32 and 0.37 log units for bis(L-leucinato)copper(II) and bis(L-methionato)copper(II), respectively. The disagreement for amino acid complexes with apical coordination appeared to be 0.44 ($CuSer_2$), 0.18 ($CuThr_2$), and 0.92 ($CuTrp_2$, I = 0.1 mol L^{-1}) log units. Stability constants of aromatic amino acids were also fairly well reproduced, yielding the residual value (log units) from 0.01 and 0.00 (regr. 5) for $Cu(Phe)_2$ to 0.02 (regr. 7) for $Cu(Tyr)_2$.

For the estimation of the second constant of ligation, we chose a set of 27 log K_2 values for 10 binary and 17 ternary copper(II) complexes with the naturally occurring amino acids taken from the literature.[45–48]

Correlation (Table III) is not very dependent on the kind of topological index, but again the third-order valence-connectivity index ($^3\chi^v$) gave the best results. Indices of all molecular species (L, ML or ML_2) yielded in all cases reasonably good values of the regression coefficient (R = 0.694–0.756) and root-mean-square deviation (rms = 0.17–0.19 log units), however models which are based on the graph of complex species appear to yield slightly better results (compare regr. 3 and 4). In general, better agreement with the experiment was obtained for aliphatic amino acids than for the aromatic ones (0.23 *vs*. 0.18 for regr. 1, 0.25 *vs*. 0.19 for regr. 3, 0.21 *vs*. 0.17 for regr. 6, Table III). In virtually all cases, our method yielded better agreement

TABLE III

Multiple regression of log K_2 on topological indices of 27 copper(II) chelates with amino acids[a,b]

No.	x_1	Slope	x_2	Slope	Intercept	R	rms
1	D(A)	–0.014(7)	D(L)	0.032(7)	6.703(117)	0.711	0.19
2	D^v(A)	–0.010(4)	D^v(L)	0.022(4)	6.598(136)	0.746	0.17
3	$^1\chi^v$(A)	–0.13(5)	$^1\chi^v$(L)	0.23(5)	6.724(127)	0.696	0.19
4	$^1\chi^v$(MA)	–0.33(8)	$^1\chi^v$(MAL)	0.22(4)	6.572(167)	0.711	0.18
5	$^2\chi^v$(MA)	–0.42(11)	$^2\chi^v$(MAL)	0.29(6)	6.248(214)	0.694	0.19
6	$^3\chi^v$(MA)	–0.58(12)	$^3\chi^v$(MAL)	0.49(7)	6.017(214)	0.756	0.17
7	W(MA)	–0.003(1)	W(MAL)	0.0010(1)	6.907(63)	0.719	0.18

[a] K_2 = [MAL] $[MA]^{-1}$ $[L]^{-1}$; A and L denote ligands (amino acids). Standard errors are given in parentheses; the set of stability constants was taken from Ref. 8.

[b] D, the sum-delta molecular connectivity index; χ, the valence-connectivity index; W, the Wiener index.

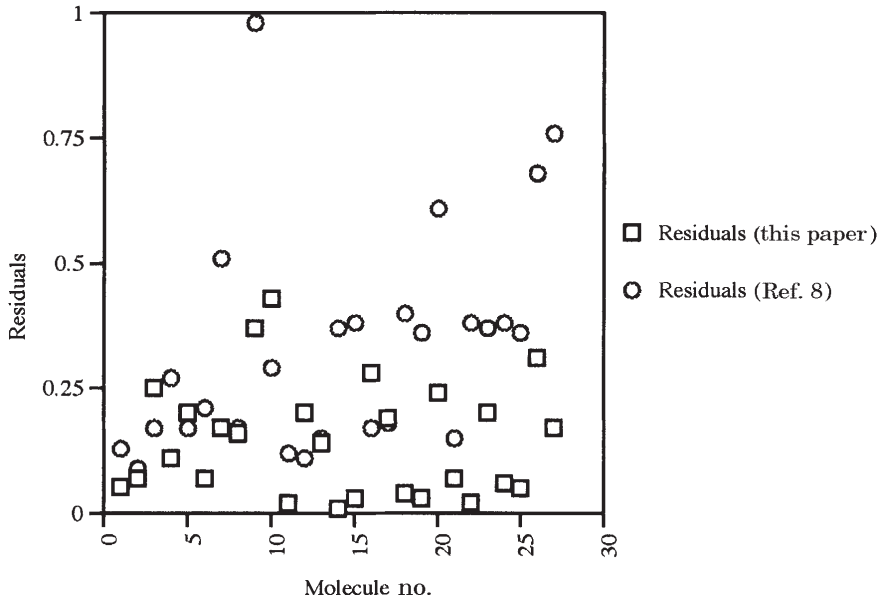

Figure 2. Absolute values of the differences between the calculated and measured values of log K_2 (□, regression 4, Table II; O, calculated from mechanistic considerations[8]): (1) Gly/Gly, (2) Ala/Ala, (3) Ser/Ser, (4) Val/Val, (5) Thr/Thr, (6) Leu/Leu, (7) Phe/Phe, (8) Tyr/Tyr, (9) Trp/Trp, (10) Met/Met, (11) Gly/Ala, (12) Gly/Ser, (13) Gly/Thr, (14) Gly/Tyr, (15) Gly/Phe, (16) Ala/Ser, (17) Ala/Thr, (18) Ala/Tyr, (19) Ala/Phe, (20) Val/Tyr, (21) Ser/Thr, (22) Ser/Tyr, (23) Ser/Phe, (24) Thr/Tyr, (25) Thr/Phe, (26) Tyr/Phe, (27) Tyr/Trp.

with the experimental data than the mechanistic method of M. Tabata and M. Tanaka on the same set of log K_2 values (rms = 0.39 log units).[8]

The best regression (6, Figure 2) yielded the difference between the measured and calculated values in the range of 0.01 (Gly/Phe) to 0.31 log units (Ala/Ser). It has also to be noted that the models gave the best results for non-polar aliphatic amino acids (model 6: rms = 0.10, range 0.05–0.17, $N = 5$).

The less satisfactory agreement between theory and experiment in the case of multiple regression in comparison with regressions presented in Table II could be attributed to the less homogeneous data in the former. Stability constants for multiple regression were measured at different ionic strengths and some of the amino acids included in multiple regressions are terdentate (Ser, Thr, Trp).[49]

In conclusion, we can state that topological indices proved to be capable of providing a fairly good estimate of the stability of structurally related complex compounds. In some cases (regr. 6, Table II), the estimate nearly

reached the precission of the measurement. Moreover, the discrepancy between the measured and predicted values could be a good indication of apical coordination, or some other »unexpected« interactions.

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SAŽETAK

Procjena konstanti stabilnosti miješanih kompleksa aminokiselina s bakrom(II) iz topoloških indeksa

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Logaritmi konstanti stabilnosti binarnih i ternarnih kompleksa pet prirodnih aminokiselina (Gly, Ala, Val, Phe, Tyr) s bakrom(II) korelirani su s Wienerovim brojem (W) i Randićevim indeksima (χ) njihovih kompleksa ML_2, pri čemu je dobiven korelacijski koeficijent (r) u rasponu od 0,931 do 0,997 i korijen srednje vrijednosti kvadrata odstupanja (rms) izračunatih od izmjerenih vrijednosti u rasponu od 0,013 do 0,065. Multipla regresija 27 konstanti vezivanja drugog liganda za binarne i ternarne komplekse 10 aminokiselina (Gly, Ala, Val, Leu, Ser, Thr, Met, Phe, Tyr, Trp) prema topološkim indeksima različitih molekulskih vrsta (L, ML, ML_2) dala je koeficijent multiple korelacije (R) u rasponu od 0,696 do 0,756 i rms od 0,17 do 0,19. Rezultati su bitno bolji od rezultata dobivenih mehanističkom metodom M. Tabate i M. Tanake (Ref. 8) na istom skupu podataka (rms = 0,39). Metoda se pokazala osjetljivom na tendenciju aminokiselina prema dodatnoj (apikalnoj) koordinaciji, no ne i prema drugim strukturnim svojstvima (aromatičnosti, polarnosti). Od svih iskušanih modela, najboljima su se pokazali modeli s valencijskim indeksom povezanosti trećega reda ($^3\chi^v$) izračunanog iz formule za kompleksne spojeve (ML i ML_2).