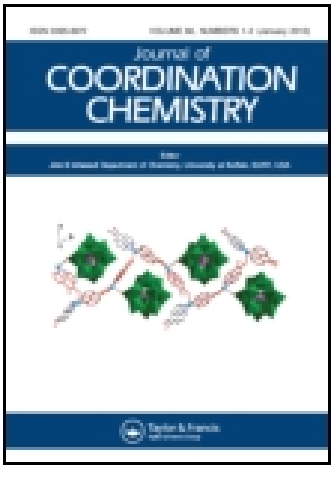

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Stability prediction of copper(II) complexes with peptides containing cysteinic disulfide bridge by models based on the connectivity index $^{3}\chi^{v}$

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Stability prediction of copper(II) complexes with peptides containing cysteinic disulfide bridge by models based on the connectivity index $^3\chi^v$

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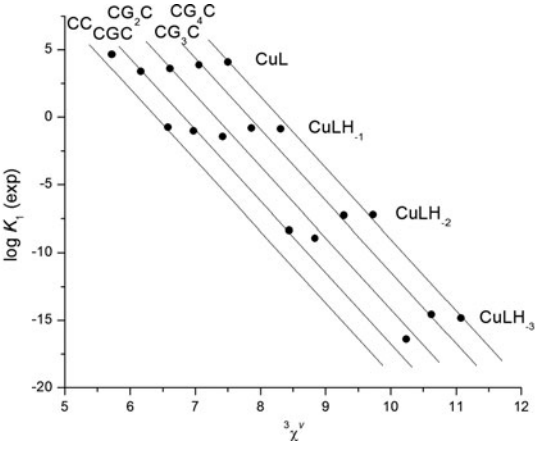

The article is a continuation of our work on the modeling of the stability of complex compounds. For copper(II) complexes with five protonated and deprotonated cyclic oligopeptides containing a disulfide bridge, we developed two common models. The variables used in both models are valence molecular connectivity index of the third order, $^3\chi^v$, and indicator variable(s), *In* or In_1 and In_2. The model with In_1 and In_2 (they represent the number of terminal and non-terminal glycine residues, respectively) yielded better estimates ($S.E._{cv} = 0.51$) than the model with *In* ($= In_1 + In_2$); $S.E._{cv} = 0.60$.

Keywords: Coordination compounds; Oligopeptides; Stability constants; Topological indices

1. Introduction

Connectivity indices, as all graph-theoretical indices [1–4], are derived from molecular graphs, and molecular graphs are derived from constitutional formulas. Despite the correlation, the molecular graph does not match entirely to constitutional formulas. Namely, for

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coordination compounds, connectivity of atoms in molecular graphs does not necessarily correspond to their bonding. In the models for the prediction of stability constants of coordination compounds from their connectivity index of the third order, ${}^3\chi^v$ [5, 6], we introduced additional bonds with the metal to simulate interactions with side chains [7], or excluded weaker metal–ligand bonds [8, 9]. Moreover, the molecular graph can be divided into sub-graphs, from which separate ${}^3\chi^v$ variables were derived [10], or the complexes in the same series could be modeled as coordinated by various numbers of waters [11]. Such flexibility in defining molecular graphs enabled us, among others, to suggest an anomalous way of binding, e.g. binding tendency of 2-hydroxybutanoic acid in its *mono*-complex with cadmium(II) [12].

Our articles are devoted to the interactions of heavy metals with bioligands. This chemically poorly defined, but very important class of compounds encompasses chelates of biogenic amines, amino acids, oligopepties, and nucleotides as well as their mixed complexes [13–16].

However this article is aimed at modeling of a peculiar kind of these compounds, namely peptides cyclized over a cysteinic disulfide bridge. The five simplest peptides of this kind, CC, CGC, CG_2C, CG_3C, and CG_4C (C and G stands for cystine and glycine, respectively), as well as their copper(II) complexes, were investigated by glass electrode potentiometry and UV–Vis spectroscopy [17, 18]. They were studied as model compounds for copper(II) interactions with peptide hormones containing disulfide bridges, vasopressin and oxytocin [19–21]. However, from our point of view, it is interesting to see if our simple models could be applied to such a complex system.

2. Methods

2.1. *Calculation of topological indices*

All of the models were developed using the ${}^3\chi^v$ index (the valence molecular connectivity index of the third order), which was defined as [4, 22–25]:

$$ {}^3\chi^v = \sum_{\text{path}} [\delta(i)\delta(j)\delta(k)\delta(l)]^{-0.5} \tag{1} $$

where $\delta(i)$, $\delta(j)$, $\delta(k)$, and $\delta(l)$ are weights (valence values) of vertices (atoms) i, j, k, and l making up the path of length 3 (three consecutive chemical bonds) in a vertex-weighted molecular graph. The valence value, $\delta(i)$, of vertex i is defined as:

$$ \delta(i) = [Z^v(i) - H(i)]/[Z(i) - Z^v(i) - 1] \tag{2} $$

where $Z^v(i)$ is the number of valence electrons belonging to the atom corresponding to vertex i, $Z(i)$ is its atomic number, and $H(i)$ is the number of hydrogens attached to it.

The ${}^3\chi^v$ index for all complexes was calculated from their graphic representations, assuming that Cu(II) is four-coordinate (figure 1). The details of the calculations were given in our previous article [7].

3. Results and discussion

In this article, we deal with the stability constants ($\log K_1$) of copper(II) *mono*-complexes with cyclic oligopeptides containing a cysteinic disulfide bridge (figure 1). All $\log K_1$ values

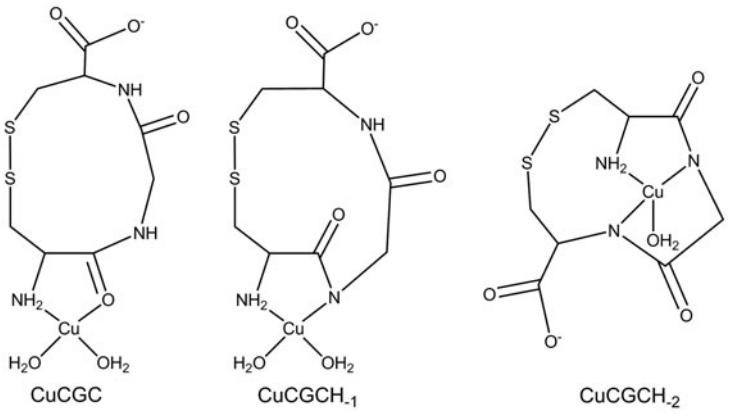

Figure 1. Constitutional formulas of protonated and deprotonated CuCGC complexes from which graph representations, needed for topological indices calculation, were deduced.

Table 1. The logarithms of experimental ($T = 298.2$ K, $I = 0.1$ mol dm^{-3}) K_1 values for Cu(II) complexes with five protonated and deprotonated oligopeptides, their $^3\chi^v$ index and indicator variables (In, In_1, In_2).

Complex	log K_1	$^3\chi^v$	In	In_1	In_2
CuCC	4.66	5.722	0	0	0
CuCGC	3.40	6.164	1	1	0
$CuCG_2C$	3.60	6.61	2	2	0
$CuCG_3C$	3.88	7.056	3	2	1
$CuCG_4C$	4.09	7.502	4	2	2
$CuCCH_{-1}$	−0.75	6.578	0	0	0
$CuCGCH_{-1}$	−1.01	6.971	1	1	0
$CuCGCH_{-2}$	−8.34	8.442	1	1	0
$CuCG_2CH_{-1}$	−1.45	7.418	2	2	0
$CuCG_2CH_{-2}$	−8.91	8.835	2	2	0
$CuCG_2CH_{-3}$	−16.40	10.238	2	2	0
$CuCG_3CH_{-1}$	−0.82	7.864	3	2	1
$CuCG_3CH_{-2}$	−7.27	9.281	3	2	1
$CuCG_3CH_{-3}$	−14.58	10.627	3	2	1
$CuCG_4CH_{-1}$	−0.88	8.31	4	2	2
$CuCG_4CH_{-2}$	−7.23	9.727	4	2	2
$CuCG_4CH_{-3}$	−14.84	11.073	4	2	2

for complexes with CC, CGC, CG_2C, CG_3C, and CG_4C (table 1) have been taken from the same article [18], which provides experimental data of high quality needed for proper calibration of our models.

The dependence of log K_1 on the $^3\chi^v$ index of Cu(II) complexes with four protonated oligopeptides (figure 2) shows an ascending trend from CuCGC to $CuCG_4C$ (figure 2; $r = 0.998$, $S.E._{cv} = 0.03$). Unfortunately, because of its exceptionally high stability, the CuCC complex does not fit the correlation.

The dependence of log K_1 of Cu(II) complexes with oligopeptides and their deprotonated forms ($N = 17$) on the $^3\chi^v$ index is depicted in figure 3. Closer inspection of the figure reveals that for each peptide, i.e. Cu(II) complexes with its protonated and deprotonated forms, a linear correlation of stability *versus* $^3\chi^v$ index can be obtained. These linear

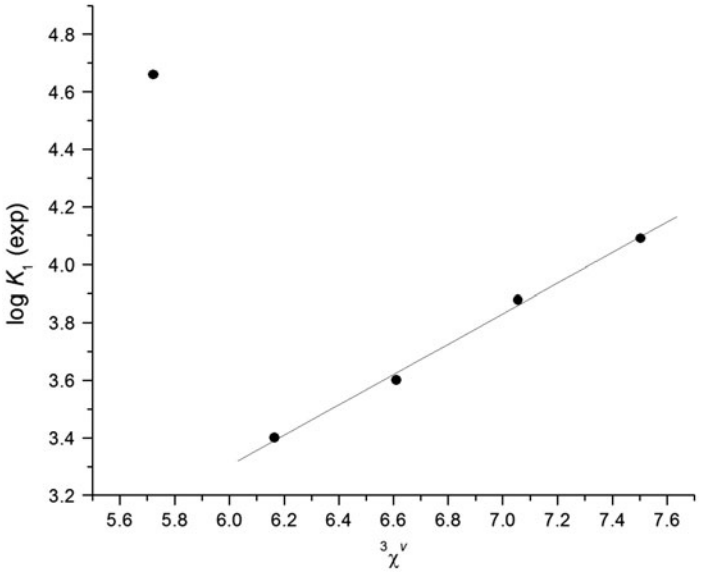

Figure 2. Experimental log K_1 *vs.* $^3\chi^v$ index for Cu(II) complexes with five oligopeptides. The regression line depicts the correlation on four complexes (Model 1, table 2).

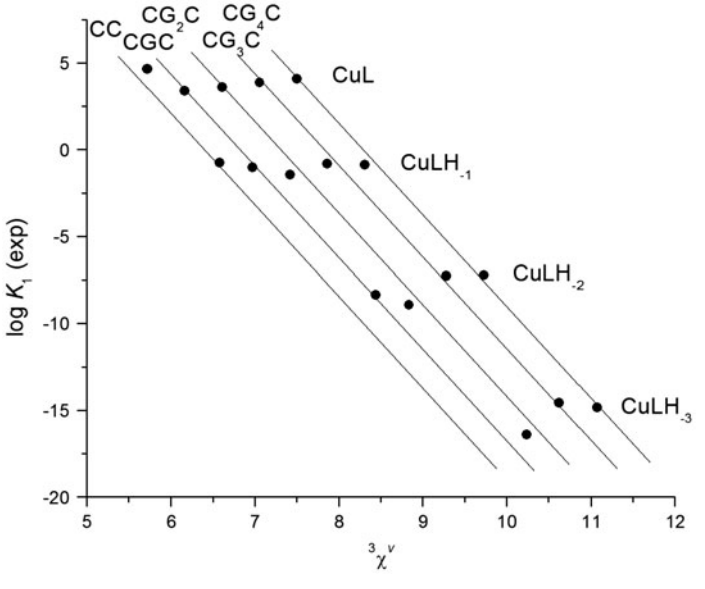

Figure 3. Experimental log K_1 *vs.* $^3\chi^v$ index for Cu(II) complexes with protonated and deprotonated oligopeptides. For each peptide complex, approximated linear dependence of log K_1 *vs.* $^3\chi^v$ is depicted by the line.

Table 2. Regression models for estimation of the log K_1 of Cu(II) complexes with peptides.

Model	N	Regression coefficients a_1(S.E.)	a_2(S.E.)	b(S.E.)	r	S.E.	S.E.$_{cv}$
1	4	–0.527(24)		0.14(16)	0.998	0.02	0.03
2	3	–5.13(12)		34.93(90)	0.9997	0.20	–
3	4	–5.46(12)		39.4(10)	0.9995	0.24	0.51
4	4	–5.08(15)		39.6(13)	0.999	0.29	0.52
5	4	–5.19(20)		42.8(18)	0.999	0.38	0.69
6	16	–5.26(11)	2.54(13)	33.23(78)	0.997	0.49	0.60
7	13	–5.131(80)	2.396(91)	32.70(55)	0.999	0.31	0.39

regressions have correlation coefficients of 0.9985 to 0.9997 and slopes from −5.08 to −5.46 (Models 2–5, table 2). However, the regression slope for the two CC complexes was significantly different (–6.32), obviously due to the exceptional stability of CuCC.

Virtually the same slopes enabled development of the common model using the indicator variable *In*:

$$\log K_1 = a_1\ {}^3\chi^v + a_2\, In + b \tag{3}$$

The model proved successful for estimation of stability constants for all complexes studied except for CuCC (Model 6, table 2; $N = 16$). The largest errors of estimates, 0.73, 0.73, and 0.84, were for CG_2CH_{-1}, CG_2CH_{-2}, and CG_2CH_{-3} complexes, respectively. This was expected because these complexes have log K_1 values lower than predicted from assumed parallel lines (figure 3), i.e. the regression for CG_2C complexes has the steepest slope (Model 3, table 2). However, by exclusion of these three complexes, we obtained the model with $r = 0.999$ and S.E.$_{cv} = 0.39$ (Model 7, table 2; figure 4).

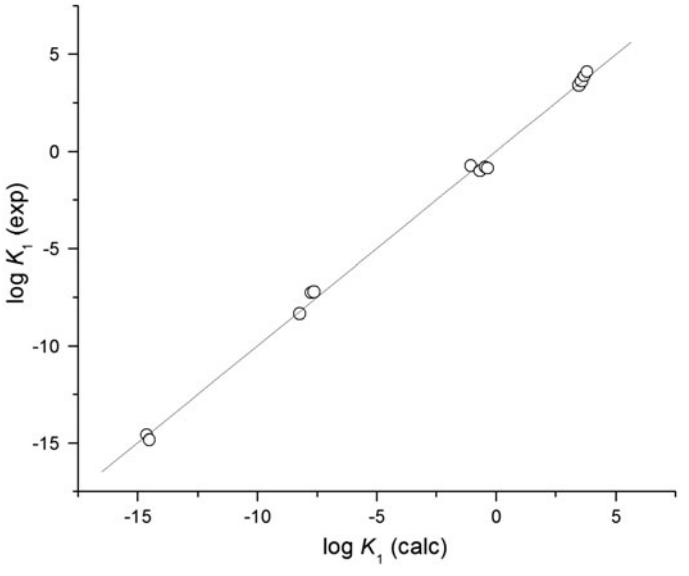

Figure 4. Experimental *vs.* theoretical log K_1 values for Cu(II) complexes with 13 protonated and deprotonated oligopeptides (Model 7, table 2).

If the indicator variable, *In*, is perceived as a number of glycine residues, it could be decomposed into two indicator variables, the first for terminal (bonded to cysteine, In_1) and the second for non-terminal glycines (not bonded to cysteine, In_2). The obtained model:

$$\log K_1 = 34.12(66) - 5.250(96)^3\chi^v + 1.83(22)In_1 + 2.87(17)In_2 \quad (4)$$

yielded $r = 0.998$, S.E = 0.43, and $S.E._{cv} = 0.57$ if applied to all complexes ($N = 17$). After exclusion of the CuCC complex $S.E._{cv}$ drops to 0.51, better than the cross-validated error of the model with one indicator variable (Model 6, table 2).

4. Conclusion

Predicted stability of copper(II) complexes with peptides containing disulfide bridges are generally in accord with the other predictions obtained by models based on the connectivity index $^3\chi^v$. The typical $S.E._{cv}$ values for these models are 0.3–0.5 log K units, but for well-defined systems they can drop to $S.E._{cv} < 0.1$ [12]. For peptide complexes, we obtained $S.E._{cv} = 0.22$–0.42 using the models with indicator variable, and $S.E._{cv} = 0.16$–0.19 with models based on the segmentation of molecule [10, 26]. However, some substantial problems remain. The first is exceptional stability of the CuCC complex, the other is the "anomalous" behavior of the CG_2C complexes. (In [18], the authors assumed coexistence of two different 3N complexes for the $CuCG_2C$ system.)

The first problem we tried to solve by proposing a different coordination in CuCC, assuming binding of copper(II) to a disulfide bridge (modeled as a single sulfur) instead of to the carbonyl group. In that way, we obtained $^3\chi^v$ (CuCC) = 8.759, which fits well the regression line ($r = 0.998$, S.E. = 0.03, $S.E._{cv} = 0.05$; $N = 5$). This model is not in disagreement with the experimental finding that supports the transient sulfur donation in the copper(II)-glypressin, i.e. GlyGlyGlyLys(8) – vasopressin [21] and Cu(II)/oxidized glutathione system [27], as well as with X-ray structures of Cu(II) and Ni(II) complexes with disulfide ligands [28–32], but the suggested interaction seems to be weak (e.g. log K_1 ($CuMe_2S_2$) = 0.49) [33]. However, the new value of $^3\chi^v$ does not fit the common model [equation (3)], neither is the hypothesis in accord with the anomalously high pK_2 of CC [17].

The answer to the problem lies possibly in the structure, i.e. conformation, of the ligands. X-ray structure reveals the *cis*-peptide bond in the CC molecule [34], whereas for other ligands *trans*-conformation is favored [35]. Results from CD-spectroscopy of Boc-CG_nC-OMe peptides suggest strong electronic disulfide–amide interaction, but only for CGC and CG_2C derivatives [35]. There is also a possibility that the effect could be attributed to solvent–solute interactions, but our, essentially empirical, method could not cope with such subtle interactions. Our method is based on a comparison of structure and property of chemically related compounds, not on explicit calculations of intra- or intermolecular interactions.

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