

Short communication

Estimation of Stability of Cadmium(II) *Mono-Complexes* with Monodentate and Bidentate Ligands by Models Based on ${}^3\chi^v$ Connectivity Index

Ante Miličević* and Nenad Raos

Institute for Medical Research and Occupational Health, Ksaverska c. 2, HR-10001 Zagreb, Croatia

* Corresponding author: E-mail: antem@imi.hr

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Abstract

Based on the quadratic function used previously for the estimation of copper(II) amino acid *mono-complexes*, we developed the model for the estimation of the stability constant K_1 of cadmium(II) complexes with five amino acids (glycine, alanine, 2-aminobutanoic, 2-aminopentanoic, and 2-aminohexanoic acid). The model gave $R^2 = 0.960$ and S.E. = 0.03. Also, for the first time we proposed (univariate linear) model for the estimation of K_1 of complexes with monodentate ligands, namely the Cd(II) complexes with methanoic, ethanoic, propanoic, 2-methylpropanoic, butanoic, 2-methylbutanoic, 2-hydroxyethanoic, 2-hydroxypropanoic and 2-hydroxybutanoic acid. The model is capable to discriminate monodentate from bidentate ligands; much better statistic was obtained ($R^2 = 0.966$ and S.E. = 0.05) if 2-hydroxybutanoic acid was assumed to be bidentate.

Keywords: Stability constants, Coordination compounds, Theoretical models, Topological indices, 2-Hydroxycarboxylic acids, Amino acids

1. Introduction

To develop a model for the prediction of stability constants of coordination compounds¹ is not an easy task; stability of coordination compounds is determined by many adverse factors (inductive and steric effects, additional (secondary) coordination, interaction with solute etc.) and to propose a general and universally valid model which would take into account all these factors for the complexes of various ligands with various metals seems virtually impossible. In such a complicated situation it appears most fruitful to try solving the problem by the way of analogy, *i.e.* to start from the classical position that structurally similar compounds behave similarly.

The quantitative measure of structural (constitutional) similarity are topological indices,^{2–6} and among them the valence connectivity index of the 3rd order (${}^3\chi^v$) proved best for the prediction of stability constants of coordination compounds.^{7–9} Therefore we developed models for the prediction of the stability constants (K_1 , K_2 , and β_2) of metal (Cu^{2+} , Ni^{2+} , Co^{2+} , Fe^{2+} , Mn^{2+}) complexes with variety of ligands (amino acids, their derivatives, diamines, triamines, and peptides), based on ${}^3\chi^v$ index of various

molecular species.^{9,10} We especially paid attention on graph representations of the molecular species (defining the number of water molecules in a complex,⁸ additional bonding of the side chain to metal ion,^{8,11} subtraction of „aninfluential bondings“,^{12,13} and segmentation of the molecular graph^{14,15}), rather than on using various topological indices, which is quite unusual in the QSPR approach. In such a way it was possible to separate factors which are influential, from the factors which are not, in determining the stability of the complex. It was clearly demonstrated that a more realistic graph („constitutional formula“) led to better agreement between the theory and experiment.⁸ It has also to be pointed out that despite its simplicity, our approach is capable to reproduce experimental results with the error of $\log K < 0.1$; it was found suitable even for discussion of the quality of experimental results.¹⁶

In this paper we are going to apply our model on new systems, *i.e.* cadmium(II) *mono-complexes* with amino acids and, for the first time, to the *mono-complexes* of monocarboxylic and 2-hydroxycarboxylic acids (for the estimation of K_2 and β_2 of Cd(II) aminoacidates see Ref. 17). Amino acids are bidentate ligands forming five-membered chelate ring, monocarboxylic acids are mono-

dendate ligands, and 2-hydroxycarboxylic acids are ligand with dubious coordination (monodentate or bidentate). The aim of this contribution is therefore to answer the question is it possible by our method to discriminate monodentate from bidentate ligands and to find out the limits and scope of our previously developed models.

2. Methods

2.1. Calculation of Topological Indices

We calculated topological indices using a program system E-DRAGON, developed by R. Todeschini and co-workers, which is capable of yielding 119 topological indices in a single run, along with many other molecular descriptors.^{18,19} Connectivity matrices were constructed with the aid of the *Online SMILES Translator and Structure File Generator*.²⁰

All models were developed by using the ${}^3\chi^v$ index (the valence molecular connectivity index of the 3rd order), which was defined as:^{5,21–23}

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

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 a vertex i is defined by:

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

where $Z^v(i)$ is the number of valence electrons belonging to the atom corresponding to vertex i , $Z(i)$ is its atomic

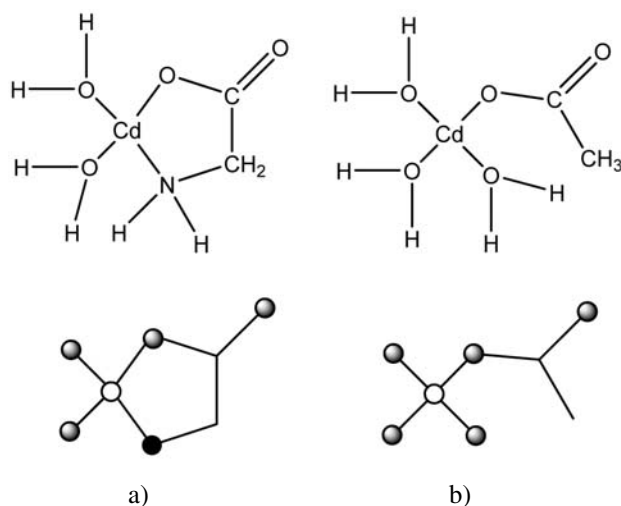


Fig. 1. Constitutional formula and graph representation of cadmium(II) *mono*-complexes with a) amino acid (glycine) and b) carboxylic acid (ethanoic acid). Heteroatoms are marked with ○ (Cd), ● (N), and ● (O).

number, and $H(i)$ is the number of hydrogen atoms attached to it. It has to be pointed out that ${}^3\chi^v$ is only a member of the family of valence connectivity indices ${}^n\chi^v$, which differ between each other by the path length, *i.e.* the number of δ 's in the summation term, Eq. 1.

The ${}^3\chi^v$ index for all *mono*-complexes were calculated from the graph representations of *aqua*-complexes (Fig. 1), assuming that metal in *mono*-complexes is tetra-coordinated.⁹

2.2. Regression Calculations

Regression calculations, including the leave-one-out procedure (LOO) of cross validation were done using the CROMRsel program.²⁴ The standard error of cross validation estimate is defined as:

$$\text{S.E.}_{\text{cv}} = \sqrt{\sum_i \frac{\Delta X_i^2}{N}} \quad (3)$$

where ΔX and N denotes cv residuals and the number of reference points, respectively.

3. Results and Discussion

Dependence of $\log K_1$ on ${}^3\chi^v$ (Figure 2) for cadmium(II) complexes with five amino acids (glycine, alanine, 2-aminobutanoic, 2-aminopentanoic, and 2-amino-hexanoic acid) shows non-linear relationship (Table 1, Figure 2):

$$\log K_1 = a_1[{}^3\chi^v(\text{ML})]^2 + a_2[{}^3\chi^v(\text{ML})] + b \quad (4)$$

yielding $R^2 = 0.960$ and $\text{S.E.}_{\text{cv}} = 0.13$ (Model 1 in Table 3, Figure 2).

It is in accordance with the same conclusion for copper(II) *mono*-complexes with nine amino acids,²⁵ and, also, with the finding that $\log K_1$ of Cu(II) and Ni(II) complexes with the “cadmium(II) set” of amino acids²⁶ show the same trend (Figure 3). This suggests the interplay of two effects. One is positive, presumably inductive (caused by alkyl substituent electron donation), and the other is negative, presumably steric. Though $\text{p}K$ values of those ligands shows the basicity is rising from glycine to 2-ami-

Table 1. Experimental values of $\text{p}K_1$ and $\text{p}K_2$ for five amino acids, along with $\log K_1$ ($t = 25^\circ\text{C}$, $I = 3 \text{ mol dm}^{-3}$) and ${}^3\chi^v$ index of their Cd(II) complexes^{27,28}

No.	Amino acids	$\text{p}K_1$	$\text{p}K_2$	$\log K_1$	${}^3\chi^v(\text{ML})$
1	Glycine (G)	2.76	9.68	4.01	2.436
2	Alanine (A)	2.81	9.72	3.69	2.921
3	2-Aminobutanoic acid (AB)	2.79	9.73	3.64	3.125
4	2-Aminopentanoic acid (AP)	2.81	9.75	3.72	3.285
5	2-Aminohexanoic acid (AH)	2.86	9.76	3.74	3.554

nohexanoic acid (Table 1), the $\log K_1$ values decrease from glycine to 2-aminobutanoic acid complex.^{27,28} This indicates that destabilizing effect is much more pronounced during the complexation with alanine and, especially, 2-aminobutanoic acid. Contrary, for the complexation of 2-aminopentanoic and 2-aminohexanoic acid with Cd(II) inductive effect prevails over the steric effect.

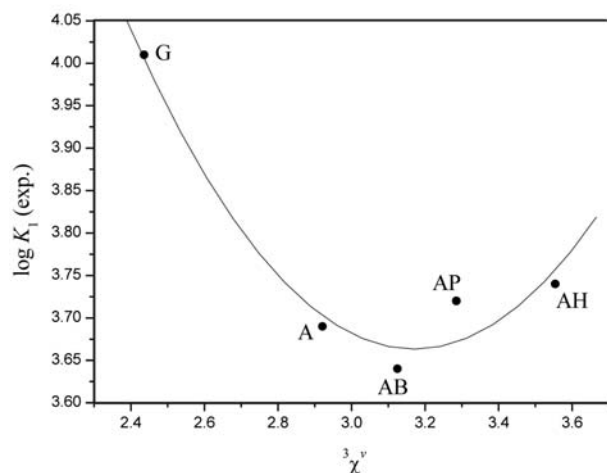


Figure 2. Plot of the dependence of experimental $\log K_1$ stability constants on ${}^3\chi^v$ index for Cd(II) *mono*-complexes with α -amino acids ($N=5$, Table 1). The curve corresponds to Model 1 (Table 3).

On the other hand, dependence of $\log K_1$ on ${}^3\chi^v$ for Cd(II) complexes with the nine carboxylic acids (methanoic, ethanoic, propanoic, 2-methylpropanoic, butanoic, 2-methylbutanoic, 2-hydroxyethanoic, 2-hydroxypropanoic and 2-hydroxybutanoic acid) is linear (Table 2, Model 2 in Table 3, Figure 4). The regression gave positive slope ($R^2 = 0.966$ and $S.E._{cv} = 0.06$), which is quite unusual regarding our previous models on bidentate and tridentate ligands (diamines, amino acids and triamines) where slope was negative.⁹

Table 2. Experimental values of pK for four *monocarboxylic*, two 2-methylcarboxylic and three 2-hydroxycarboxylic acids, along with $\log K_1$ ($t = 25^\circ\text{C}$, $I = 3 \text{ mol dm}^{-3}$) and ${}^3\chi^v$ index of their Cd(II) complexes²⁷

No.	Carboxylic acids	pK	$\log K_1$	${}^3\chi^v$ (ML)
1	Methanoic (M)	3.75	1.30	0.768
2	Ethanoic (E)	4.89	1.43	1.014
3	Propanoic (P)	5.06	1.56	1.200
4	2-Methylpropanoic (MP)	5.01	1.69	1.338
5	Butanoic (B)	5.04	1.57	1.366
6	2-Methylbutanoic (MB)	4.97	1.90	1.881
7	2-Hydroxyethanoic (HE)	3.70	1.36	1.041
8	2-Hydroxypropanoic (HP)	3.82	1.63	1.208
9	2-Hydroxybutanoic (HB)*	4.14	2.31	2.521

* Bidentate ligand

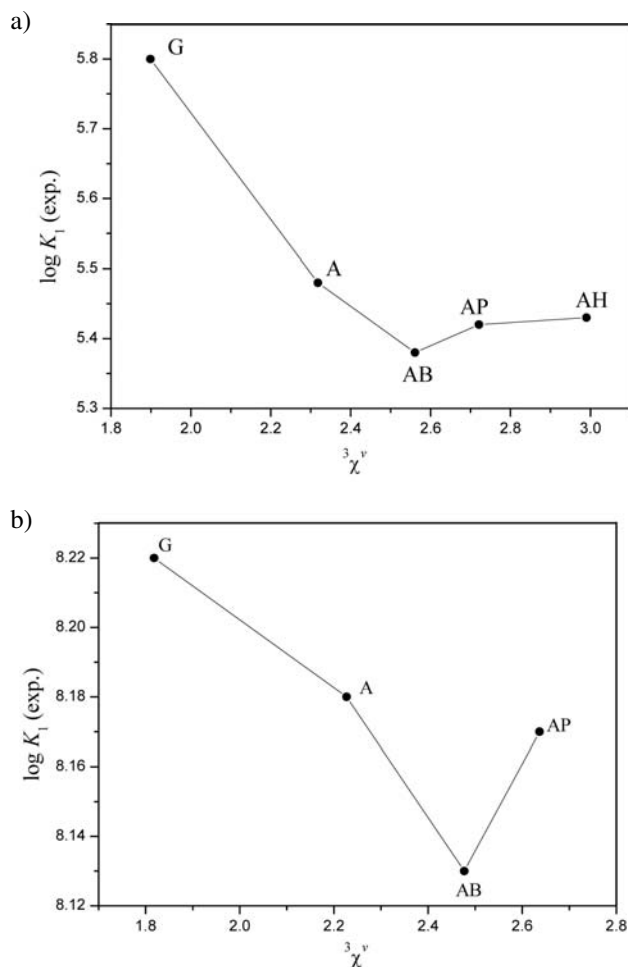


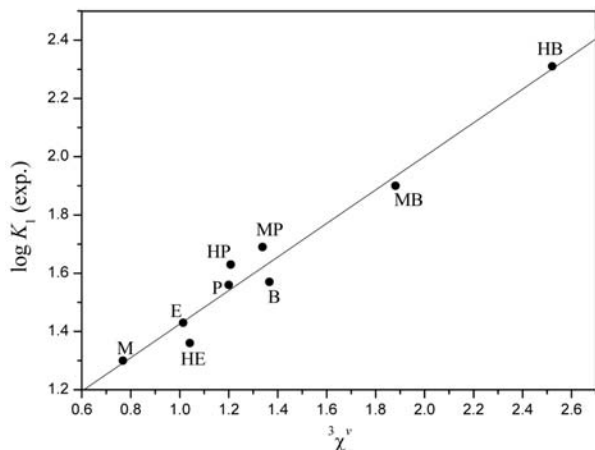
Figure 3. Plots of the dependence of experimental $\log K_1$ stability constants on ${}^3\chi^v$ index for a) five Ni(II) and b) four Cu(II) *mono*-complexes with α -amino acids.²⁶

Comparing the stability constants of carboxylic acid complexes with those of amino acids, one can see that the main difference between them lies in the first three members of homologous series. While for complexes with amino acids $\log K_1$ decreases from glycine to 2-aminobutanoic acid, for carboxylic acids stability is rising continuously. This suggests that for complexation of monodentate ligands, such as carboxylic acids, with Cd(II) inductive effect is bigger for every subsequent *monocarboxylic* acid, and especially for 2-methylcarboxylic and 2-hydroxycarboxylic acids.

Although most of the acids in Table 2 are monodentate ligands, 2-hydroxycarboxylic acids have also a hydroxyl group which is capable of coordinating to the central metal ion. It is so especially when electron density on hydroxyl oxygen is larger due to the inductive effect originating from the alkyl group, as in the case of 2-hydroxybutanoic acid complex.²⁷ Therefore, for calculation of ${}^3\chi^v$ index of Cd(II) complex with 2-hydroxybutanoic acid we applied graph representation in which ligand is bidentate, forming the five-membered chelate ring with Cd(II). The

Table 3. Regression models for the estimation of the $\log K_1$ of Cd(II) mono-complexes

Model	N	Ligands	Regression coefficients			R^2	S.E.	S.E. _{cv}
			a_1 (S.E.)	a_2 (S.E.)	b (S.E.)			
1	5	Amino acids	0.63(13)	-4.02(80)	10.0(12)	0.960	0.03	0.13
2	9	Carboxylic acids		0.576(41)	0.850(59)	0.966	0.05	0.06

**Figure 4.** Plot of the dependence of experimental $\log K_1$ stability constants on $3\chi^v$ index for Cd(II) mono-complexes with carboxylic acids ($N = 9$, Table 2). The line corresponds to Model 2 (Table 3).

assumption is confirmed by the comparison of the Model 2 with the model in which all 2-hydroxycarboxylic ligands were assumed to be bidentate. The model gave $R^2 = 0.475$ and $S.E._{cv} = 0.29$, and the model in which all 2-hydroxycarboxylic ligands were taken as monodentate gave $R^2 = 0.605$ and $S.E._{cv} = 0.26$. This is substantially worse than our original Model 2 ($R^2 = 0.966$, $S.E._{cv} = 0.06$).

4. Conclusion

Beside the substantial difference in magnitude of the stability of cadmium(II) complexes with monodentate and bidentate ligands, there is also a qualitative difference in their homologous series. While for amino-acid complexes the value of K_1 descends for the first three members in the homologous series, the stability of carboxylic acid complexes ascends continuously.

Although hydroxyl group is formally capable of coordinating to the central metal ion, our theoretical analysis show that the agreement between the theory and experiment is possible if additional bonding is assumed only for cadmium(II) complex with 2-hydroxybutanoic acid. This assumption is in line with previous, more qualitative discussion.²⁷ All these point to two conclusions. First, our models are capable of discriminating monodentate from bidentate ligands, and, second, graph derived from structural formula is a genuine representative of the properties of the complex.

5. Acknowledgement

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6. References

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Povzetek

Na osnovi kvadratne funkcije, ki smo jo uporabili že za oceno stabilnosti bakrovih(II) amino kislinških *mono*-kompleksov, smo razvili model za oceno stabilnostnih konstant K_1 kadmijevih(II) kompleksov s petimi aminokislinami (glicinom, alaninom, 2-aminobutanojsko, 2-aminopentanojsko in 2-aminoheksanojsko kislino). Statistični parametri modela so $R^2 = 0.960$ in S.E. = 0.03. Predlagali smo tudi (univariatni linearni) model za oceno K_1 kompleksov z monodentatnimi ligandi kot so Cd(II) kompleksi z metanojsko, etanjsko, propanojsko, 2-metilpropanojsko, butanojsko, 2-metilbutanojsko, 2-hidroksietanojsko, 2-hidroksipropanojsko in 2-hidroksibutanojsko kislino. Model je sposoben razlikovati monodentatne od bidentatnih ligandov; statistični parametri modela so se zelo izboljšali ($R^2 = 0.966$ and S.E. = 0.05), če smo upoštevali 2-hidroksibutanojsko kislino kot bidentatno.