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Scientific paper

Prediction of Stability Constants of Zinc(II) Complexes with 2-aminobenzamide and Amino Acids

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Abstract

We developed a model for the stability (log β_{ZnLB}) of Zn^{2+} mixed complexes (N = 16) with 2-aminobenzamide (L) and four amino acids (B) glycine, alanine, valine, and phenylalanine at 300, 310, 320, and 330 K. The model based on the quadratic regression function of the molecular valence connectivity index of the third order, $^3\chi^v$, yielded S.E. = 0.02. We also developed an overall model for K_1, K_2 and β_{ZnLB} of the same system at all of the four temperatures (N = 48). This model yielded S.E. = 0.05.

Keywords: coordination compounds, stability constants, graph-theoretical indices, regression models, models in chemistry

1. Introduction

Although models based on graph theoretical indices rely on somewhat vague concepts, as do other models based on topological approaches in theoretical chemistry,[1,2] they have proved quite successful in many applications. Graph theoretical indices correlate well with many physicochemical parameters[3–6] and biological activities (QSAR).[7,8] Our efforts to use topological indices, especially the valence connectivity index of the 3rd order, $^3\chi^v$, in order to build regression models for the prediction of stability constants of coordination compounds[9] ended with varying success, depending on the nature of coordination compounds as well as on the quality of experimental data. Stability constants of copper(II) complexes with α-amino acids were reproduced with such a precision that it was even possible to evaluate the results of two electroanalytical methods (GEP and SWV) used for their measurement.[10] For copper(II) complexes with derivatives of thioflavin T and clioqiunol, used as model compounds for the study of Alzheimer's disease, we obtained even better results[11] than those achieved by the more demanding DFT method.[12] In some cases, our method, despite being strictly empirical, enabled the analysis of coordination, *i.e.* it gave insight into the structure of the complex.[13,14] However, in other cases additional variables[15] and unusual forms of regression functions[16] had to be introduced in order to obtain an acceptable agreement between theory and experiment.

The topic of this contribution are mixed zinc(II) complexes of 2-aminobenzamide (2-AB) with amino acids. These complexes have already been studied by pH-metric and spectrophotometric methods,[17] because 2-aminobenzamide and its derivatives have desirable pharmacological properties,[18] and are also used as analytical reagents.[19] On the other hand, zinc(II) participates in many biological processes,[20] so the study of the above mentioned complexes should lead to a better understanding of the pharmacokinetics of 2-aminobenzamide and its derivatives.

Besides the model for stability (β_{ZnLB}) of mixed complexes of 2-aminobenzamide (L) with Zn^{2+} and four amino acids (B) glycine, alanine, valine, and phenylalanine at different temperatures (300, 310, 320, and 330 K):

$$\beta_{ZnLB} = \frac{[ZnLB^+]}{[Zn^{2+}][L][B^-]} \quad (1)$$

we developed an overall model for β_{ZnLB}, K_1 and K_2, defined as:

$$K_1 = \frac{[ZnB^+]}{[Zn^{2+}][B^-]} \quad (2)$$

$$K_2 = \frac{\left[\mathrm{ZnLB^+}\right]}{\left[\mathrm{ZnL^{2+}}\right]\left[\mathrm{B^-}\right]} \quad (3)$$

2. Methods

2. 1. Calculation of Topological Indices

We calculated topological indices using the E-DRAGON program system, developed by R. Todeschini and coworkers, capable of yielding 119 topological indices in a single run, along with many other molecular descriptors.[21,22] Connectivity matrices were constructed with the aid of the *Online SMILES Translator and Structure File Generator*.[23]

The valence molecular connectivity index of the 3rd order, $^3\chi^v$, was defined as:[24–27]

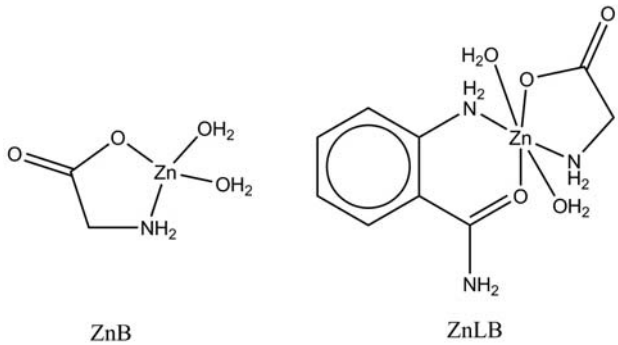
$$^3\chi^v = \sum_{\text{path}} [\delta(i)\ \delta(j)\ \delta(k)\ \delta(l)]^{-0.5} \quad (4)$$

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:

$$\delta(i) = [Z^v(i) - H(i)]/[Z(i) - Z^v(i) - 1] \quad (5)$$

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 hydrogen atoms attached to it.

The $^3\chi^v$ index for all *mono*- and mixed complexes was calculated from the graph representations of *aqua*-complexes (Fig. 1), assuming that the metal in the *mono*-complexes is tetracoordinated and in mixed complexes hexacoordinated.



ZnB ZnLB

Figure 1. Constitutional formulas of Zn(II) tetracoordinated *mono*complexes with glycine (B) and hexacoordinated mixed complex with 2-aminobenzamide (L) and glycine (B)

2. 2. Regression Calculations

Regression calculations, including the leave-one-out procedure (LOO) of cross validation were done using the CROMRsel program.[28] The standard error of the cross-validation estimate was defined as:

$$\mathrm{S.E._{cv}} = \sqrt{\sum_i \frac{\Delta X_i^{\,2}}{N}} \quad (6)$$

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

3. Results

In order to model the logarithm of stability constant, log β_{ZnLB}, (Eq. 1, Table 1) of mixed Zn^{2+}complexes with 2-aminobenzamide and amino acids (ZnLB), we used the quadratic function of $^3\chi^v$ (Figure 2):

Table 1. Experimental stability constants log K_1, log K_2 and log β_{ZnLB} [17] and $^3\chi^v$ index of Zn(II) complexes with 2-aminobenzamide (L) and amino acids (B)

Temperature (K)	Amino acid (B)	log K_1	log K_2	log β_{ZnLB}	$^3\chi^v$ (ZnB)	$^3\chi^v$ (ZnLB)
300	Gly	4.96	5.29	9.13	1.748	5.770
	Ala	4.89	5.13	8.97	2.148	6.082
	Val	4.59	4.83	8.67	2.599	6.533
	Phe	4.46	4.68	8.52	3.581	7.195
310	Gly	4.84	5.22	8.95	1.748	5.770
	Ala	4.76	5.06	8.79	2.148	6.082
	Val	4.46	4.80	8.53	2.599	6.533
	Phe	4.33	4.66	8.39	3.581	7.195
320	Gly	4.73	5.18	8.81	1.748	5.770
	Ala	4.65	5.01	8.64	2.148	6.082
	Val	4.36	4.73	8.36	2.599	6.533
	Phe	4.24	4.59	8.22	3.581	7.195
330	Gly	4.61	5.08	8.63	1.748	5.770
	Ala	4.56	4.94	8.49	2.148	6.082
	Val	4.23	4.67	8.22	2.599	6.533
	Phe	4.13	4.54	8.09	3.581	7.195

$$\log \beta_{ZnLB} = a_1[^3\chi^v(ZnLB)] + a_2[^3\chi^v(ZnLB)]^2 + b \quad (7)$$

because it proved better than the linear function (*e.g.* at 300 K, S.E. = 0.04 and 0.06 for quadratic and linear function, respectively; $N = 4$).

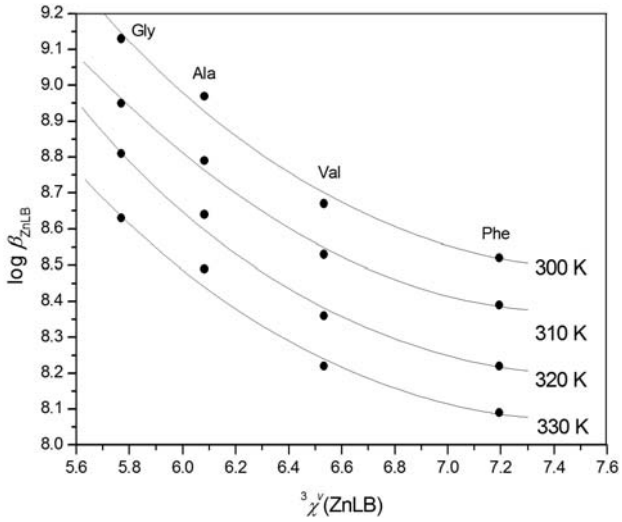


Figure 2. Quadratic dependence of log β_{ZnLB} of mixed Zn^{2+}complexes with 2-aminobenzamide and amino acids (ZnLB) on their $^3\chi^v$ index, at four temperatures.

As the dependence of log β_{ZnLB} on temperature in the range 300–330 K is linear,[17] we proposed the model for all four of the temperatures ($N = 16$) simply by including temperature into Eq. (7):

$$\log \beta_{ZnLB} = a_1[^3\chi^v(ZnLB)] + a_2[^3\chi^v(ZnLB)]^2 + a_3T + b \quad (8)$$

where T is the absolute temperature at which constants, log β_{ZnLB}, were measured. The model yielded $S.E._{cv}$ = 0.03 (Model 1, Table 2).

The values of log K_1 and log K_2 (Eqs. 2 and 3) show the same quadratic dependence on $^3\chi^v$ (Figure 3). This enabled the development of the model ($N = 12$) for all of the constants at a given temperature:

$$\log K = a_1{}^3\chi^v + a_2[^3\chi^v]^2 + a_3[\log K_0] + b \quad (9)$$

where K denotes K_1, K_2 and β_{ZnLB}; K_0 are the corresponding stability constants of a referent complexes (either with glycine, alanine, valine, or phenylalanine); $^3\chi^v$ denotes $^3\chi^v$(ZnB) in the case of K_1 constant and for K_2 and β_{ZnLB} it corresponds to $^3\chi^v$(ZnLB) normalized on $^3\chi^v$(ZnGly):

$$^3\chi^v = {}^3\chi^v(ZnLB) - [{}^3\chi^v(ZnLGly) - {}^3\chi^v(ZnGly)] \quad 10)$$

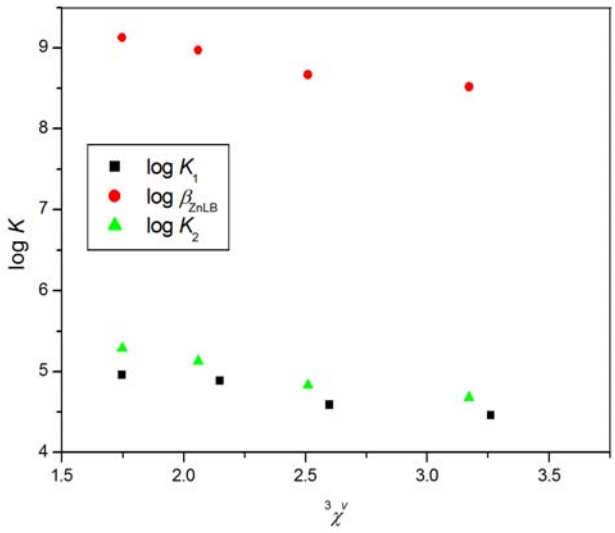


Figure 3. The dependence of log K (log K_1, log K_2 and log β_{ZnLB}) on $^3\chi^v$ at 300 K; $^3\chi^v$ denotes $^3\chi^v$(ZnB) in the case of K_1 constant and for K_2 and β_{ZnLB} constants $^3\chi^v$ is $^3\chi^v$(ZnLB) normalized on $^3\chi^v$(ZnB), Eq. (10).

Taking glycine complexes as referent, the model gave $S.E._{cv}$ = 0.09 (Model 2, Table 2).

The same function, Eq. (9), can be applied to K_1, K_2 and β_{ZnLB} at all four of the temperatures ($N = 48$). In this case, K_0 denotes the corresponding stability constants of a referent complexes at all of the temperatures. Taking glycine complexes as referent, the model gave $S.E._{cv}$ = 0.06 (Model 3, Table 2).

Furthermore, we have found that it is possible to make the model more predictive. To be more precise, it is enough to know the K_0, *i.e.* K_1, K_2 and β_{ZnLB} constants of a referent complex at only two temperatures. The K_0 values at the other two temperatures can be then easily calculated from the linear dependence of K_1, K_2 and β_{ZnLB} on T. This way, fewer experimental constants are needed for

Table 2. Regression models for the estimation of stability constants log K_1, log K_2 and log β_{ZnLB} of Zn(II) complexes with 2-aminobenzamide (L) and amino acids (B)

Model (Eq.)	Stability constant	N	Regression coefficients				r	S.E.	$S.E._{cv}$
			a_1(S.E.)	a_2(S.E.)	a_3(S.E.)	b(S.E.)			
1 (8)	β_{ZnLB}	16	–3.22(41)	0.216(32)	–0.0155(6)	25.2(13)	0.9960	0.02	0.03
2 (9)	K_1, K_2, β_{ZnLB}	12	–1.26(43)	0.171(87)	0.987(11)	1.78(52)	0.9995	0.06	0.08
3 (9)	K_1, K_2, β_{ZnLB}	48	–1.22(17)	0.167(34)	0.9880(43)	1.72(20)	0.9996	0.05	0.06

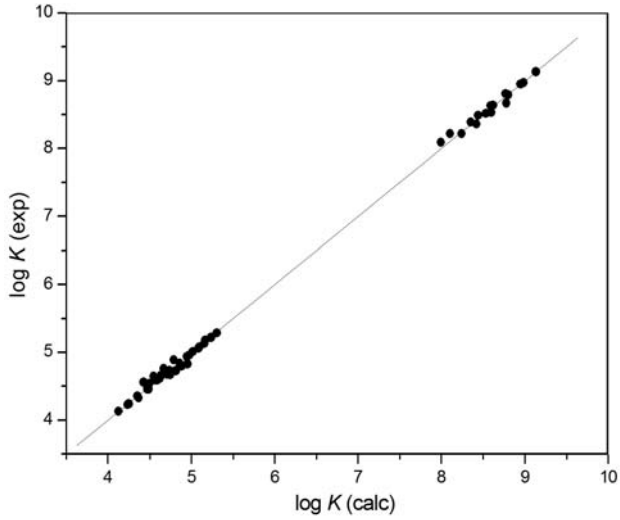


Figure 4. Experimental vs. calculated values of K (K_1, K_2 and $\beta_{Zn\text{-}LB}$) by Eq. (9), where K refer to the stability of glycine complexes at 300 and 310 K. The model yielded r = 0.9996, S.E. = 0.05, $S.E._{cv}$ = 0.06.

calibration. Such a model, calibrated on K_1, K_2 and β of glycine complexes at 300 and 310 K, yielded $S.E._{cv}$ = 0.06 (Figure 4).

4. Conclusion

We developed two kinds of models. A model for the prediction of stability (log β_{ZnLB}) of Zn^{2+} mixed complexes with 2-aminobenzamide (L) and four amino acids (B) at four temperatures (N = 16), and a model for the prediction of K_1, K_2 and β_{ZnLB} of the same system (N = 48). In both cases, the theoretical results showed excellent agreement with the experimental ones, yielding errors commensurable with the errors of measurements. Specifically, the maximal differences between the experimental and theoretical (cross-validated) values were 0.06 and 0.15 for the two models (Models 1 and 3, Table 2), respectively, while the declared standard error of measurements were 0.03–0.08 for log K_1 and 0.03–0.09 for log β_{ZnLB}.

It should also be pointed out that the log K_1 function has the same form as the function for copper(II) *mono*-complexes with amino acids.[29]

5. References

1. P. L. Ayers, R. J. Boyd, P. Bultinck, M. Caffarel, R. Carbó-Dorca, M. Causá, J. Cioslowski, J. Contreras-Garcia, D. L. Cooper, P. Coppens, C. Gatti, S. Grabowski, P. Lazzeretti, P. Macchi, A. M. Pendás, P. L. A. Popelier, K. Ruedenberg, H. Rzepa, A. Savin, A. Sax, W. H. E. Schwarz, S. Shahbazian, B. Silvi, M. Solà, V. Tsirelson, *Comput. Theor. Chem.* **2015**, *1053*, 2–16. http://dx.doi.org/10.1016/j.comptc.2014.09.028
2. E. V. Babaev, Intuitive chemical topology concepts, in: D. Bonchev, R. Rouvray, (Eds.), Chemical Topology: Introductions and Fundamentals, Gordon and Breach, Reading, 1999, pp. 167–264.
3. Z. Mihalić, N. Trinastić, *J. Chem. Educ.* **1992**, *69*, 701–712. http://dx.doi.org/10.1021/ed069p701
4. B. Lučić, S. Nikolić, N. Trinajstić, *Croat. Chem. Acta* **1995**, *68*, 417–434.
5. E. V. Konstantinova, M. V. Diudea, *Croat. Chem. Acta* **2000**, *73*, 383–403.
6. M. Randić, S. C. Basak, M. Pompe, M. Novič, *Acta Chim. Slov.* **2001**, *48***,** 169–180.
7. L. H. Hall, L. B. Kier, Eur. *J. Med. Chem.* **1981**, *16*, 399–407.
8. S. Bajaj, S. S. Sambi, A. K. Madan, *Croat. Chem. Acta* **2005**, *78*, 165–174.
9. N. Raos, A. Miličević, *Arh. Hig. Rada Toksikol.* **2009**, *60*, 123–128. http://dx.doi.org/10.2478/10004-1254-60-2009-1923
10. N. Raos, G. Branica, A. Miličević, *Croat. Chem. Acta* **2008**, *81*, 511–517.
11. A. Miličević, N. Raos, *Arh. Hig. Rada Toksikol.* **2013**, *64*, 539–545. http://dx.doi.org/10.2478/10004-1254-64-2013-2418
12. A. Rimola, J. Alí-Torres, C. Rodríguez- Rodríguez, J. Poater, E. Matito, M. Solá, M. Sodupe*, J. Phys. Chem.* A **2011**, *115*, 12659–12666. http://dx.doi.org/10.1021/jp203465h
13. A. Miličević, N. Raos, *Acta Chim. Slov.* **2012**, *59*, 194–198.
14. A. Miličević, N. Raos, General model based on connectivity index $^3\chi^v$ for the prediction of stability constants of copper(II) complexes with α-amino acids, in: I. Gutman (Ed.), Topics in Chemical Graph Theory, Univ. Kragujevac, Kragujevac, 2014, pp. 193–204.
15. A. Miličević, N. Raos, *Acta Chim. Slov.* **2014**, *61*, 904–908.
16. A. Miličević, N. Raos, *Croat. Chem. Acta* **2009**, *82*, 633– 639.
17. J. Dharmaraja, P. Subbaraj, T. Esakkidurai, S. Shobana, S. Raji, *Acta Chim. Slov.* **2014**, *61*, 803–812.
18. D. Oltmanns, M. Eisenhut, W. Mier, U. Heberkorn, *Curr. Med. Chem.* **2009**, *16*, 2086–2094. http://dx.doi.org/10.2174/092986709788612684
19. S. B. Katiyar, I. Bansal, J. K. Saxena, P. M. Chauhan, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 47–50. http://dx.doi.org/10.1016/j.bmcl.2004.10.046
20. B. L. Vallee, K. H. Falchuk, *Physiol. Rev.* **1993**, *73*, 79–118.
21. I. V. Tetko, J. Gasteiger, R. Todeschini, A. Mauri, D. Livingstone, P. Ertl, V. A. Palyulin, E. V. Radchenko, N. S. Zefirov, A. S. Makarenko, V. Y. Tanchuk, V. V. Prokopenko, , *J. Comput. Aid. Mol. Des.* **2005**, *19*, 453–63. http://dx.doi.org/10.1007/s10822-005-8694-y
22. VCCLAB, Virtual Computational Chemistry Laboratory, http://www.vcclab.org, 2005.
23. http://cactus.nci.nih.gov/services/translate/
24. L. B. Kier, L. H. Hall, *J. Pharm. Sci.* **1976**, *65*, 1806–1809. http://dx.doi.org/10.1002/jps.2600651228
25. L. B. Kier, L. H. Kall, Molecular Connectivity in Structure-

Activity Analysis, Willey, New York, 1986.
26. L. B. Kier, L. H. Hall, Molecular Connectivity in Chemistry and Drug Research, Academic Press, New York, 1976.
27. M. Randić, *MATCH Commun. Math. Comput. Chem.* **2008**, *59*, 5–124.
28. B. Lučić, N. Trinajstić, *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 121–132. http://dx.doi.org/10.1021/ci980090f
29. A. Miličević, N. Raos, *Chin. J. Chem.* **2011**, *29*, 1800–1804. http://dx.doi.org/10.1002/cjoc.201180316

Povzetek

Razvili smo model za stabilnost (log β_{ZnLB}) Zn^{2+} mešanih kompleksov (N = 16) z 2-aminobenzamidom (L) in štirimi amino kislinami (B): glicinom, alaninom, valinom in fenilalaninom pri 300, 310, 320 in 330 K. Model je osnovan na kvadratni regresijski funkciji molekularnega indeksa valenčne povezljivosti tretjega reda, $^3\chi^v$. Za isti sistem smo postavili tudi splošni model za K_1, K_2 in β_{ZnLB} pri vseh temperaturah.