Prediction of Stability of Copper(II) and Nickel(II) Complexes with Fructose-Amino Acids from the Molecular Graph Models Developed on Amino Acid Chelates*

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Keywords
connectivity indices
stability constants
coordination compounds
Amadori rearrangement products
fructose-glycine
fructose-valine
fructose-leucine
fructose-isoleucine
fructose-phenylalanine

Topological analysis was applied for the estimation of stability constants of copper(II) and nickel(II) mono- (K_1) and bis-complexes (β_2) with fructose-amino acid adducts ($N = 5$). Calibration models were built by correlating the of stability constants of Cu^{II} and Ni^{II} mono- and bis-complexes with α-amino acids on their $^3\chi^v$ connectivity index. The bivariate regression with the indicator variable ($In = 1$ for Cu, $In = 0$ for Ni) was also applied. By averaging the theoretically obtained values, log K_1 values of fructose-amino acids were estimated with the *rms* error of 0.22 and 0.27 log K units for Cu and Ni chelates, respectively. The best estimates of log β_2 values yielded the *rms* error of 0.76 and 0.75 log β units for Cu and Ni chelates, respectively. However, the results for nickel(II) bis-chelates were improved by the introduction of explicit interaction of amino acid side chains with fructose moiety, yielding *rms* = 0.34 log β units.

INTRODUCTION

There are many ways of estimating stability constants of coordination compounds, from simple empirical rules (Irving-Williams order,[1] cation classifications,[2,3] distinction of »hard« and »soft« Lewis acids and bases, HSAB[4,5]) to quantitative models, which differ considerably both in the theoretical basis and the level of sophistication. Models based on »interaction parameters« between atoms in the first coordination sphere[6–8] were followed by the molecular-mechanics[9–13] and molecular-dynamics[14] approaches, along with the methods based on continuous distribution of solvents[15,16] and the overlapping spheres (OS) models.[17–20]

Among the methods applied for estimation of stability constants of coordination compounds are also those based on molecular graph theory (or on topological indices derived from it). These methods have found wide application in all branches of chemistry, starting from the classical problems of boiling points[21–23] and properties of conjugated systems[24–26] to the estimation of biological activities (QSAR) and drug design.[27–31] In coordination chemistry, protonation constants of *N*-alkylated and *N,N*-dialkylated glycines were successfully correlated to their Wiener and Randić indices, as well as the stability constants of their ML (log K_1, *i.e.*, log β_1) and ML$_2$, chelates (log β_2).[32,33] Later, the method was applied in estimation of stability constants of copper(II) chelates with

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nine naturally occurring amino acids, reproducing stability constants of mono-complexes with an *S.E.* = 0.07 log *K* units.[34] Stability constants of their binary and 16 ternary complexes were consecutively reproduced with an *S.E.* of 0.13 and 0.14 log β units, respectively.[34,35] It was found that the success of the estimate was not determined only by the topological index applied (Randić $^3\chi^v$ index proved best), but also by the choice of molecular species (ligand, chelate or aquated chelate).[34,35] For instance, estimation of log K_1 values for copper(II) chelates with *N*-alkylated glycines yielded *S.E.*$_{cv}$ equal to 0.62 and 0.37 log *K* units for $^3\chi^v$(L) and $^3\chi^v$(ML^{aq}) representation, respectively.[34]

The crucial problem of a topological approach is the structural homogeneity of the set, *i.e.*, the question whether stability constants of structurally different complexes should be estimated by the same topological model. In our recent paper,[36] we have shown that stability constants for triamines could be successfully estimated from the constants for diamines, and *vice versa*. This paper aims to find out whether it would be possible to successfully estimate the stability constants of chelates of amino acid derivatives by applying calibration models derived from simple complexes with naturally occurring amino acids. For that purpose we have chosen, as test sets, first (K_1) and second (β_2) stability constants of five Cu^{II} and Ni^{II} chelates with fructose-amino acid adducts.[37] In contrast to α-amino acids, which are bidendate, their fructose adducts are tridendate ligands with stability constants differing by 1–2 log *K* units from the constants of parent compounds.

METHODS

Calculations of topological indices were performed with the program system DRAGON 2.1, written by R. Todeschini and coworkers,[38] which is capable of yielding 262 topological indices in a single run, along with many other molecular descriptors.

The connectivity matrix was constructed with the aid of the program CORINA,[39] developed by J. Sadowski, C. H. Schwab and J. Gasteiger.

All calculations were done with the Randić index $^3\chi^v$ (*the valence molecular connectivity index of the 3rd order*):[40]

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

which generally gives the most consistent results of all kinds of topological, particularly Randić ($^1\chi^v$, $^1\chi^v$, *etc.*), indices.[34,35]

In Eq. (1), $\delta(i)$, $\delta(j)$, $\delta(k)$, and $\delta(l)$ denote weights (valence-delta values) of vertices (atoms) *i*, *j*, *k*, and *l* making up the path of length 3 (three consecutive che-

mical bonds) in a vertex-weighted molecular graph.[41,42] Valence-delta value, $\delta(i)$, of a vertex *i* is defined by:

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

where $Z^v(i)$ is the number of valence electrons belonging to atom *i*, $Z(i)$ is its atomic number, and $H(i)$ is the number of hydrogen atoms attached to atom *i*. For instance, delta values for primary, secondary, tertiary and quaternary carbon atoms are 1, 2, 3, and 4, respectively; for oxygen in the OH group it is equal to 5, and for NH$_2$ group $\delta(N) = 3$.

In this paper, constitutional formulas (graphs) for amino acid chelates with two additionally coordinated water molecules, denoted ML^{aq} and ML$_2^{aq}$, were used for the calculation of the $^3\chi^v$ index for complexes in the calibration model.[34]

Regression calculations, including the leave-one-out procedure of cross validation, cv, were done using the CROMRsel program.[42] The standard error of estimate, *S.E.*, is defined as:

$$S.E. = (1/N\ \Sigma\Delta X^2)^{0.5} \qquad (3)$$

ΔX denotes the difference between experimental and calculated (fitted) values of the stability constant, and *N* is the number of complexes. In the formula for *S.E.*$_{cv}$, ΔX denotes *cv* residuals. Root-mean-square error (*rms*) was calculated by the same formula (Eq. (3)), but ΔX now denotes the difference between experimental and predicted values of the stability constant.

RESULTS AND DISCUSSION

Calibration Models

For construction of calibration lines for the estimation of stability constants of ML complexes (log K_1), we have chosen 11 copper(II) (Model 1) or nickel(II) (Model 2) complexes with α-amino acids (Table I). All the constants were measured by the same method (potentiometry) and under the same experimental conditions (25 °C, *I* = 0.05 mol L^{-1}).[8,43] In our first attempt, we used a set of 12 amino acid chelates, but obtained *r* = 0.49 (*S.E.*$_{cv}$ = 0.19 log *K* units) and *r* = 0.81 (*S.E.*$_{cv}$ = 0.13 log *K* unit) for copper(II) and nickel(II) complexes, respectively; however, after discarding isoleucine complexes, substantially better calibration lines were obtained (Figures 1 and 2). These lines yielded, as expected, a better reproduction of stability constants of the test set (see Conclusion).

By using the same set of log K_1's, the bivariate regression, with $^3\chi^v$ index and an indicator variable (*In* (CuL) = 1, *In* (NiL) = 0), was performed, yielding the calibration model for both copper(II) and nickel(II) complexes (Model 3, Table I).

The same set of amino acids was used in the univariate regression of log β_2's on $^3\chi^v$, and bivariate regression

TABLE I. Calibration models derived by regression of log K_1[(a)] on $^3\chi^v$ for copper(II) and nickel(II) mono-chelates with amino acids

Regression Model	N	Intercept (S.E.)	$^3\chi^v$ (ML^{aq}) Slope (S.E.)	Indicator variable Slope (S.E.)	r	S.E.	S.E.$_{cv}$
1	11	8.75 (17)	−0.262 (64)		0.807	0.09	0.12
2	11	6.23 (17)	−0.308 (61)		0.860	0.09	0.11
3	22	6.16 (12)	−0.285 (43)	2.649 (42)	0.998	0.09	0.11

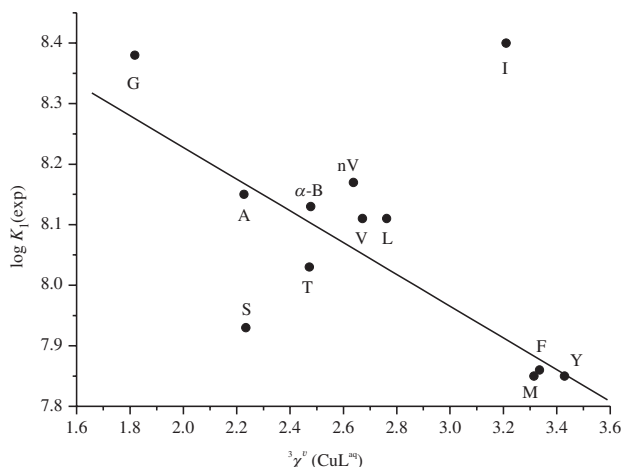[(a)] $K_1 = [ML][M]^{-1}[L]^{-1}$; L denotes amino acid, M denotes Cu^{2+} and/or Ni^{2+}

Figure 1. The calibration line (Model 1, Table I) for the estimation of stability constants of ML complexes (log K_1) of copper(II) with 9 naturally occurring amino acids (denoted by one letter code) and two non-proteinic α-amino acids, norvaline (nV) and α-aminobutyric acid (α-B). The complex with isoleucine, I, is not included in the regression. Experimental data, log K_1 (exp), were taken from Ref. 43.
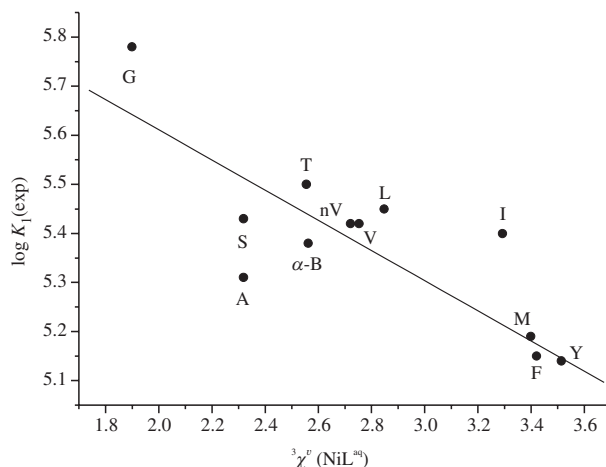
Figure 2. The calibration line (Model 2, Table I) for the estimation of stability constants of ML complexes (log K_1) of nickel(II) with 9 naturally occurring amino acids (denoted by one letter code) and two non-proteinic α-amino acids, norvaline (nV) and α-aminobutyric acid (a-B). The complex with isoleucine, I, is not included in the regression. Experimental data, log K_1 (exp), were taken from Ref. 43.

on the $^3\chi^v$ index and an indicator variable (Table II). However, the regressions lead to statistical parameters of lesser quality, especially for the copper(II) complexes (Model 4, Table II). The S.E.$_{cv}$ values were about twice higher than in the corresponding log K_1 models (Table I), which is in accordance with the results obtained by other methods (estimates of log β_2 are usually inferior to the estimates of log K_1).[34]

Test Set

As the first proof of our method, we selected copper(II) and nickel(II) mono-complexes with five fructose adducts

with naturally occurring amino acids (Tables III and IV). This class of compounds is interesting biologically[44–49] as well as chemically,[37] especially in studies of the Amadori rearrangement. From our point of view, it is important that fructose-amino acids are terdentate ligands, in contrast to the majority of amino acids which build glycinate-like structures (Figure 3).

Estimation of log K_1 constants of five copper(II) complexes with fructose-amino acids[36] from calibration lines derived from chelates of naturally occurring amino acids gave fair agreement with the experiment (Table III). The simple Model 1 and the model with indicator

TABLE II. Calibration models derived by regression of log β_2[(a)] on $^3\chi^v$ for copper(II) and nickel(II) bis-chelates with amino acids

Regression Model	N	Intercept (S.E.)	$^3\chi^v$ (ML^{aq}) Slope (S.E.)	Indicator variable Slope (S.E.)	r	S.E.	S.E.$_{cv}$
4	11	15.40 (48)	−0.094 (71)		0.401	0.20	0.25
5	11	11.26 (47)	−0.203 (67)		0.712	0.19	0.26
6	22	10.88 (35)	−0.149 (49)	4.882 (94)	0.997	0.20	0.24

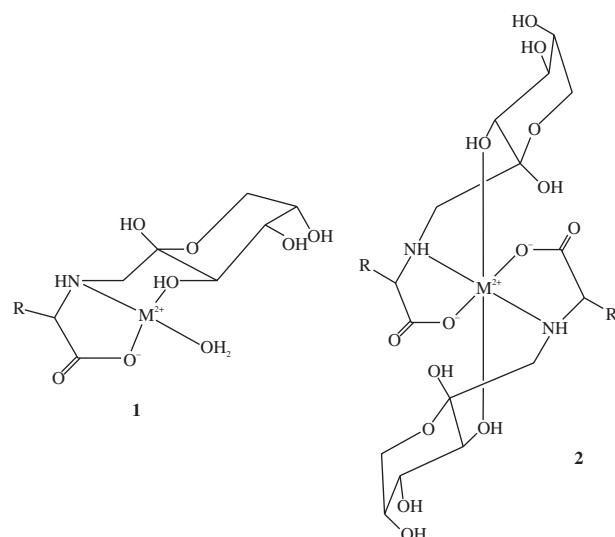[(a)] $\beta_2 = [ML_2][M]^{-1}[L]^{-2}$; L denotes amino acid, M denotes Cu^{2+} and/or Ni^{2+}

Figure 3. General formulas of mono- (**1**) and bis- (**2**) complexes (ML and ML$_2$) of fructose-amino acid adducts with metal ions (M^{2+} = Cu^{2+}, Ni^{2+}), Ref. 37.

variable, Model 3, gave virtually the same results. The same conclusion should be drawn for the analogous nickel(II) system (Table IV). However, Model 1 proved slightly better in both *rms* values (0.20 log *K* units) and the error range (0.01–0.31 log *K* units) than Model 3. By averaging the values of the models in Table III, the results were very slightly improved (*rms* = 0.22 log *K* units,

range 0.04–0.28 log *K* units), but no improvement was obtained for nickel(II) complexes. It is also noteworthy that the mean values of estimated stability constants differ 0.01–0.13 log K units from the mean of experimental values (all models in Tables III and IV), indicating that our models are essentially free from systematic error.

Predication of the log β_2 values was not so successful, especially for copper(II) complexes. Due to the poor calibration line (Model 4, Table II), stability constants of copper(II) bis-complexes were reproduced in the range of 0.93–2.64 log β units (*rms* = 1.95 log β units). The major reason for the poor agreement should be looked for in the low slope, –0.094(71), and small correlation coefficient of the calibration line (*r* = 0.401). To pass this obstacle, we estimated log β_2 (= log K_1 + log K_2) values from the calibration lines calculated for log K_1 (Model 1, Table I) and mean log K_2 experimental value for amino acid complexes (*N* = 11, < log K_2 > = 6.75 log *K* units). In this way, substantially better estimates were obtained (*rms* = 0.76, range 0.06–1.13 log β units, Table V).

Averaging the values for corrected Model 1 (Model 1a) and Model 6 led to better estimates of the *rms* value (0.71 log β units), error range (0.09–1.10 log β units) and the difference of mean values (0.48 log *K* units). The results for nickel(II) bis-complexes (Models 5 and 6, Table VI, Figure 4) are comparable to the corresponding results for copper(II) chelates (Table V). The error in Model 5 spans the range 0.43–1.29 log β units, which is compa-

TABLE III. Calculations on copper(II) mono-complexes with fructose-amino acid adducts (**1**, Figure 3)

No.	Ligand	Experimental log K_1 (Ref. 37)	Predicted log K_1 (Model 1)	Predicted log K_1 (Model 3)	Mean log K_1 (Models 1 and 3)
1	Fru-Gly	7.38	7.37	7.31	7.34
2	Fru-Val	6.83	7.14	7.06	7.10
3	Fru-Leu	7.34	7.10	7.02	7.06
4	Fru-Ile	7.22	7.00	6.91	6.95
5	Fru-Phe	7.01	6.95	6.86	6.91
mean		7.16	7.11	7.03	7.07
rms			0.20	0.24	0.22

TABLE IV. Calculations on nickel(II) mono-complexes with fructose-amino acid adducts (**1**, Figure 3)

No.	Ligand	Experimental log K_1 (Ref. 37)	Predicted log K_1 (Model 2)	Predicted log K_1 (Model 3)	Mean log K_1 (Models 2 and 3)
6	Fru-Gly	4.97	4.56	4.62	4.59
7	Fru-Val	3.91	4.29	4.37	4.33
8	Fru-Leu	4.44	4.25	4.33	4.29
9	Fru-Ile	4.04	4.12	4.22	4.17
10	Fru-Phe	4.08	4.07	4.17	4.12
mean		4.29	4.26	4.34	4.30
rms			0.27	0.28	0.27

TABLE V. Calculations on copper(II) bis-complexes with fructose-amino acid adducts (**2**, Figure 3)

No.	Ligand	Experimental log β_2 (Ref. 37)	Predicted log β_2 (Model 1a)[a]	Predicted log β_2 (Model 6)	Mean log β_2 (Models 1corr and 6)
1	Fru-Gly	13.26	12.13	13.85	12.99
2	Fru-Val	11.54	11.71	13.61	12.66
3	Fru-Leu	12.48	11.63	13.57	12.60
4	Fru-Ile	12.35	11.42	13.45	12.44
5	Fru-Phe	11.27	11.33	13.40	12.37
mean		12.18	11.64	13.56	12.61
rms			0.76	1.52	0.71

[a] $\log \beta_2 = -0.262 \, {}^3\chi^v \, (CuL^{aq}) + 15.50$

TABLE VI. Calculations on nickel(II) bis-complexes with fructose-amino acid adducts (**2**, Figure 3)

No.	Ligand	Experimental log β_2 (Ref. 37)	Predicted log β_2 (Model 5)	Predicted log β_2 (Model 6)	Predicted log β_2 (Model 5cor)	Predicted log β_2 (Model 6cor)
6	Fru-Gly	8.97	8.54	8.91	8.56	8.91
7	Fru-Val	6.91	8.20	8.67	7.47	8.11
8	Fru-Leu	7.71	8.14	8.63	7.39	8.05
9	Fru-Ile	7.28	7.97	8.51	7.31	8.00
10	Fru-Phe	7.38	7.90	8.46	7.29	7.98
mean		7.65	8.15	8.64	7.60	8.21
rms			0.75	1.15	0.34	0.70

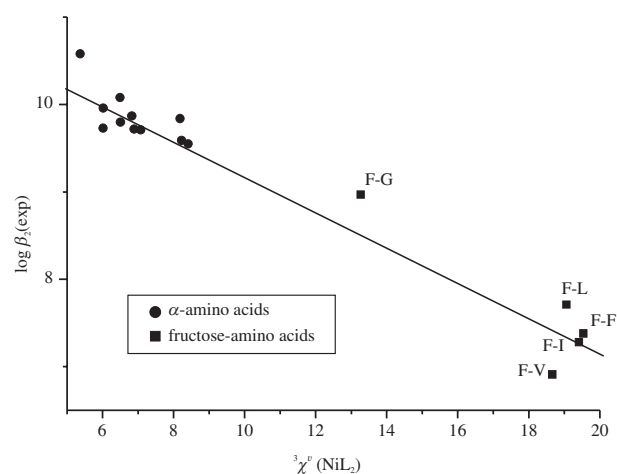
Figure 4. The calibration line (Model 5, Table II) developed for the prediction of stability constants (log β_2) of five nickel(II) complexes of the test set (ML$_2^{cor}$ representation, Table VI). Experimental data, log β_2 (exp), were taken from Ref. 37.

To improve our theoretical predictions, we introduced (in the manner of our previous models denoted as ML^{cor})[34] additional bonds connecting terminal C-atoms of amino-acid side chains with ligated (apical) –OH groups of fructose moieties. By such modeling of long-range interactions of the ligated groups, a substantial improvement of estimation was obtained (Models 5cor and 6cor, Table VI). Especially successful was the estimation obtained with Model 5cor, which reproduced all the experimental values within 0.56 log β error limits and yielded a negligible systematic error (mean difference = 0.05 log β units). Unfortunately, this model could not be applied to copper(II) bis-chelates because of the poor calibration model (No 4, Table II).

rable to the spans of Model 1a (0.06–1.13 log β units). The model with the indicator variable, Model 6, was shown again to be inferior to the simple (univariate) linear model both in *rms* deviation (1.15 log β units) and maximum error (1.76 log β units).

CONCLUSION

After comparing our theoretical estimates, we may conclude that by using calibration models developed on copper(II) and nickel(II) chelates with α-amino acids, it is possible to fairly well estimate the stability of a class of their *N*-substituted derivatives, with groups inclined to additional coordinating. The log K_1 values should be reproduced with *rms* error < 0.3 log K units by all models, and log β_2 values with *rms* = 0.34 log β units for the best model. The important factor determining the stability of

ML_2 complexes appears to be interaction of the amino-acid side chain with the fructose moiety, which can also be modeled by molecular graphs.

The validity of our approach is also supported by the finding that better calibration models (in terms of r) reproduce better the experimental constants. For instance, the calibration line for copper(II) log β_2 values ($r = 0.401$) reproduces stability constants of fructose-amino acids with $rms = 1.95$ log β units, in contrast to the analogous line for nickel(II) complexes ($r = 0.712$), which yielded rms = 0.75 log β units. Similarly, our first calibration lines (see *Calibration Models*) yielded rms error of 0.35 (r = 0.480) and 0.29 log K units ($r = 0.818$) in contrast to the lines presented in Table I, which yielded $rms = 0.20$ (r = 0.807) and 0.27 log K units ($r = 0.860$) for copper(II) and nickel(II) complexes, respectively.

REFERENCES

1. I. Irving and D. R. Williams, *J. Chem. Soc.* (1953) 3192–3210.

2. G. Schwartzenbach, *Anal. Chem.* **32** (1960) 6–9.

3. S. Ahrland, J. Chatt, and N. R. Davies, *Q. Rev. Chem. Soc.*, **12** (1958) 265–276.

4. R. G. Pearson, *J. Am. Chem. Soc.* **85** (1963) 3533–3539.

5. R. G. Pearson (Ed.), *Hard and Soft Acids and Bases,* Hutchinson and Ross, Dowden, 1973.

6. M. Tanaka, *J. Inorg. Nucl. Chem.* **35** (1973) 965–971.

7. M. Tanaka, *J. Inorg. Nucl. Chem.* **36** (1974) 151–161.

8. M. Tabata and M. Tanaka, *Inorg. Chem.* **27** (1988) 3190–3192.

9. N. Raos and V. Simeon, *J. Inorg. Biochem.* **18** (1983) 133–151.

10. N. Raos and V. Simeon, *Croat. Chem. Acta* **56** (1983) 79–85.

11. N. Raos and V. Simeon, *Croat. Chem. Acta* **57** (1984) 1217–1224.

12. J. Sabolović and N. Raos, *Polyhedron* **9** (1990) 1277–1286.

13. J. Sabolović and N. Raos, *Polyhedron* **9** (1990) 2419–1427.

14. A. Fedorovowicz, J. Mavri, P. Bala, and A. Koll, *Chem. Phys. Lett.* **289** (1998) 457–462.

15. J. Tomasi and M. Persico, *Chem. Rev.* **94** (1994) 2027–2094.

16. R. Bonaccorsi, P. Palla, and J. Tomasi, *J. Am. Chem. Soc.* **106** (1984) 1945–1950.

17. N. Raos, *Croat. Chem. Acta* **70** (1997) 913–924.

18. N. Raos, *Croat. Chem. Acta* **78** (2005) 175–180.

19. A. Miličević and N. Raos, *Croat. Chem. Acta* **78** (2005) 525–534.

20. A. Miličević and N. Raos, *Croat. Chem. Acta* **79** (2006) 281–290.

21. H. Wiener, *J. Am. Chem. Soc.* **69** (1947) 17–20.

22. S. Nikolić, N. Trinajstić, and Z. Mihalić, *Croat. Chem. Acta* **68** (1995) 105–129.

23. P. G. Seybold, M. May, and U. A. Begal, *J. Chem. Educ.* **64** (1987) 575–581.

24. A. Graovac, I. Gutman, and N. Trinajstić, *Topological approach to the chemistry of conjugated molecules. Lecture notes in chemistry,* Springer-Verlag, Berlin, Vol. 4, 1977.

25. N. Trinajstić, M. Randić, and D. J. Klein, *Croat. Chem. Acta* **68** (1995) 241–267.

26. A. Miličević, S. Nikolić, and N. Trinajstić, *J. Chem. Inf. Comput. Sci.* **44** (2004) 415–421.

27. L. B. Kier and L. H. Hall, *Molecular Connectivity in Chemistry and Drug Design*, Academic Press, New York, 1976.

28. S. Nikolić, N. Trinajstić, and Z. Mihalić, *The Detour Matrix and the Detour Index*, in: J. Devillers and A. T. Balaban (Eds.), *Topological Indices and Related Descriptors in QSAR and QSPR*, Gordon and Breach, Amsterdam, 1999, pp. 279–306.

29. S. Nikolić, M. Medić-Šarić, and J. Matijević-Sosa, *Croat. Chem. Acta* **66** (1993) 151–160.

30. A. Sabljić and N. Trinajstić, *Acta Pharm.* **31** (1981) 189–214.

31. A. Miličević, S. Nikolić, and N. Trinajstić, *Mol. Diversity* **10** (2006) 95–99.

32. B. Grgas, S. Nikolić, N. Paulić, and N. Raos, *Croat. Chem. Acta* **72** (1999) 885–895.

33. N. Raos, *Croat. Chem. Acta* **75** (2002) 117–120.

34. A. Miličević and N. Raos, *Polyhedron* **25** (2006) 2800–2808.

35. S. Nikolić and N. Raos, *Croat. Chem. Acta* **74** (2001) 621–631.

36. A. Miličević and N. Raos, *Polyhedron*, **26** (2007) 3350–3356.

37. B. Gyurcsik, T. Gajda, L. Nagy, K. Burger, A. Rockenbauer, and L. Korecz Jr., *Inorg. Chim. Acta* **214** (1993) 57–66.

38. http://www.disat.unimib.it/chm/

39. http://www.molecular-networks.com/

40. M. Randić, *J. Am. Chem. Soc.* **97** (1975) 6609–6615.

41. L. B. Kier and L. H. Hall, *Molecular Connectivity in Structure-Activity Analysis,* Wiley, New York, 1986.

42. B. Lučić and N. Trinajstić, *J. Chem. Inf. Comput. Sci.* **39** (1999) 121–132.

43. A. Gergely, I. Sovago, I. Nagypal, and R. Kiraly, *Inorg. Chim. Acta* **6** (1972) 435–439.

44. A. Abrams, P. H. Powy, and H. Borsook, *J. Am. Chem. Soc.* **77** (1955) 4794–4796.

45. A. Deifel, *Chem. Unserer Zeit* **23** (1989) 24–33.

46. E. L. F. J. Anet and T. M. Reynolds, *Aust. J. Chem.* **10** (1957) 182–192.

47. E. L. F. J. Anet, *Aust. J. Chem.* **10** (1957) 193–197.

48. T. M. Wrodnigg and B. Eder, *The Amadori and Heyns rearrangements: landmarks in the history of carbohydrate chemistry or unrecognized synthetic opportunities? Topics in Current Chemistry*, Springer, Berlin/ Heidelberg, **215** (2001) 115–152.

49. S. Fu, Min-Xin Fu, J. W. Baynes, S. R. Thorpe, and R. T. Dean, B*iochem. J.* **330** (1998) 233–239.

SAŽETAK

Predviđanje stabilnosti bakrovih(II) i niklovih(II) kompleksa s fruktoza-aminokiselinama iz modela temeljenima na molekularnim grafovima koji su razvijeni na aminokiselinskim kelatima

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Za procjenu konstanti stabilnosti bakrovih(II) i niklovih(II) monokompleksa (K_1) i biskompleksa (β_2) s aduktima fruktoze s aminokiselinama ($N = 5$) primijenjena je topološka analiza. Kalibracijski su modeli izgrađeni koreliranjem konstanti stabilnosti bakrovih(II) i niklovih(II) monokompleksa i biskompleksa s α-aminokiselinama prema njihovim indeksima povezanosti $^3\chi^v$. Upotrijebljena je također bivarijatna regresija s indikatorskom varijablom ($In = 1$ za Cu, $In = 0$ za Ni). Usrednjavanjem teorijski dobivenih vrijednosti, vrijednosti log K_1 fruktoza-aminokiselina procijenjene su s pogreškom $rms = 0,22$ log K jedinice (Cu kompleksi) i $rms = 0,27$ log K jedinice (Ni kompleksi). Najbolje procjene vrijednosti log β_2 imale su pogrešku $rms = 0,76$ za bakrove te $rms = 0,75$ log β jedinice za niklove kelate. Ipak, rezultati za niklove kelate poboljšani su uvođenjem eksplicitne interakcije aminokiselinskog pobočnog lanca za fruktoznu jedinicu, dajući $rms = 0,34$ log β jedinice.