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Modelling of copper(II) binding to pentapeptides related to atrial natriuretic factor using the $^3\chi^v$ connectivity index

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Using molecular graph theory we studied the binding of NSFRY-NH_2 and 12 related pentapeptide amides to Cu(II) as a model system for atrial natriuretic factor (ANF) peptide interactions with copper. Linear regression models based on the valence connectivity index of the 3rd order ($^3\chi^v$) reproduced experimental stability constants (log β) for 1N, 2N, 3N, and 4N coordinated complexes with the standard error of 0.30-0.39 log β units. We developed separate models for seven tyrosinic (N=28) and five non-tyrosinic peptides (N=20), and a common model for both kinds of peptides (N=48) with an indicator (dummy) variable. The results indicate additional aromatic stabilisation in 4N complexes due to metal cation-π interactions with tyrosine but not with the phenylalanine residue. We have also amended the log K and log K^* values to correct miscalculations published by Janicka-Klos et al. in 2013.

KEY WORDS: *coordination compounds; peptides; stability constants; topological indices*

Atrial natriuretic factor (ANF) is a peptide hormone secreted by the heart to control extracellular fluid volume and blood pressure by maintaining water and salt balance (1, 2). All ANF peptides have the same C-terminal sequence, NSFRY, and the same 17-residue disulphide-bonded core, which is essential for their function (1). As copper(II) deficiency leads to heart hypertrophy (3) and overproduction of ANF in the left ventricle (4), copper(II) complexes with ANF may have a protective role in heart diseases.

Using a variety of methods, Janicka-Klos et al. (5) systematically analysed Cu(II) binding to pentapeptides mimicking the *N*-terminal sequence of ANF (5). Beside NSFRY-NH_2, the peptide with the same sequence as the terminal part of ANF, they also investigated its analogues in order to see how residues of the model peptide affected Cu(II) binding. The most interesting question, however, is how copper interacts with aromatic residues, phenylalanine and tyrosine in particular. We know that cation-π interactions enhance the stability of coordination compounds such as Cu(II) chelates with amino acids (6, 7), but interactions with aromatic side chains may also include π-π stacking as well as other hydrophobic interactions (8-13).

The aim of our study was to further elucidate the behaviour of these pentapeptides. To do that, we had earlier developed a simple and efficient method to predict stability constants using regression models based on graph theory (14-25). We had also applied graph theory models on oligopeptides (n=2-5), namely on their Cu(II) and Ni(II) complexes with copolymers of glycine, aliphatic (Ala, Val, Leu, norVal, norLeu), and aromatic (Phe, Tyr) amino acid (26, 27), as well as Cu(II) complexes with peptides containing a cysteinic disulphide bridge (28).

These models proved suitable for peptides, giving the standard error of prediction of 0.2-0.3 log K units (26, 27).

METHODS

Calculation of topological indices

We calculated the topological indices using the E-DRAGON online system developed by R. Todeschini et al. (29, 30), capable of yielding 119 topological indices in a single run along with many other molecular descriptors. Connectivity matrices were constructed with the aid of Online SMILES Translator and Structure File Generator (31).

All of the models were developed using the $^3\chi^v$ index (the valence molecular connectivity index of the 3rd order), which was defined as (32-35):

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

where $\delta(i)$, $\delta(j)$, $\delta(k)$, and $\delta(l)$ are weights (valence values) of vertices (atoms) i, j, k, and l making a 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:

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

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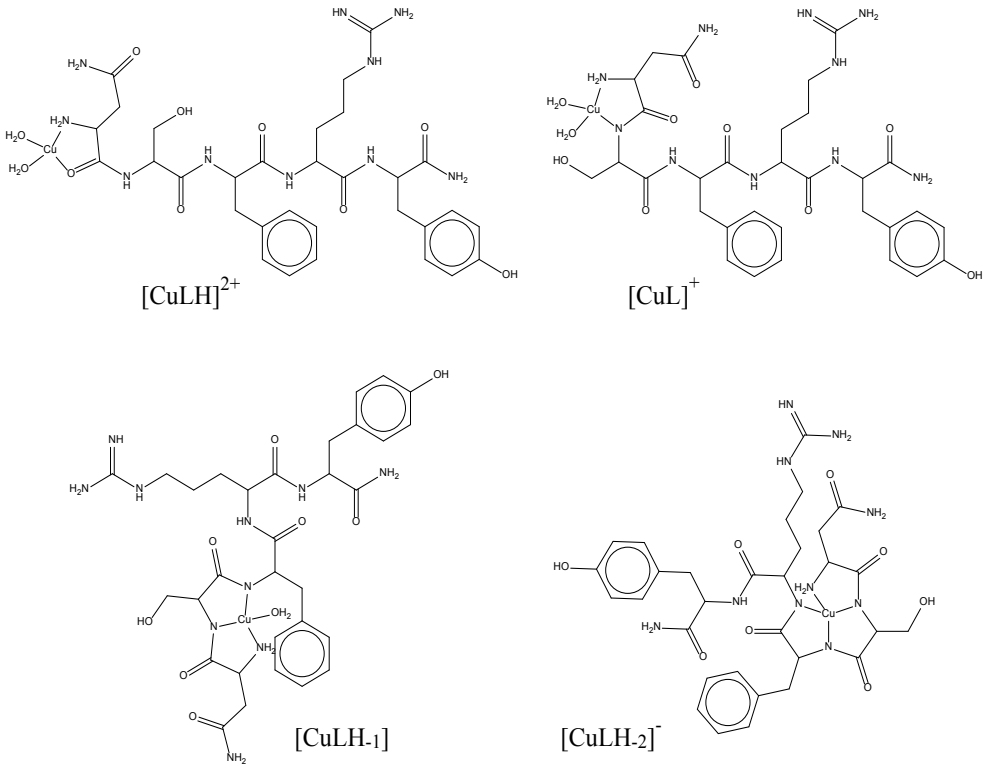

Figure 1 *Tetracoordinated Cu(II) complexes with NSFRY-NH$_2$ in its protonated and deprotonated forms*

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 was calculated for all complexes from graph representations of *aqua*-complexes under the assumption that Cu(II) is tetracoordinated (Figure 1).

Regression calculations

Regression calculations, including the leave-one-out procedure (LOO) of cross validation (cv), were done using the CROMRsel program (36). The standard error of the cross validation estimate is defined as:

$$S.E._{cv} = \sqrt{\sum_i \frac{\Delta X_i^2}{N}} \qquad [3]$$

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

RESULTS AND DISCUSSION

In order to model the stability constant (β) of Cu(II) complexes with the NSFRY-NH$_2$ peptide and its substitute analogues using $^3\chi^v$, we relied on experimental stability values reported recently by Janicka-Klos et al. (5). However, some of the values for log K and log K* were calculated erroneously. Table 1 amends the original values with our corrections (marked in bold), and reports log β and $^3\chi^v$ values.

We plotted the dependence of log β on $^3\chi^v$ (Figure 2) and found that the initial set of peptide complexes could be divided in two subsets; the subset with tyrosine residue (Subset 1, N=32) and the subset without it (Subset 2, N=20). The former subset is much more stable than the latter.

Figure 2 shows that the dependence of log β on $^3\chi^v$ is linear for the complexes of each peptide, $(CuP)^n$:

$$\log \beta = a_1[^3\chi^v(CuP)^n] + b \qquad [4]$$

where n is the charge of a complex (from +2 to -1).

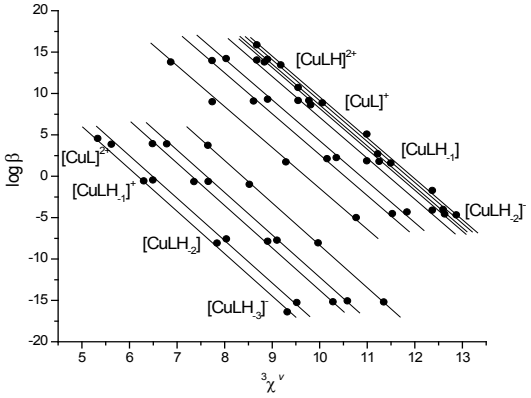

Figure 2 *Dependence of experimental log β stability constants on $^3\chi^v$ index for Cu(II) complexes with NSFRY-NH$_2$ and its analogues. Each line represents linear dependence of log β on $^3\chi^v$ for complexes of a single peptide $(CuP)^n$*

Table 1 *Experimental log β and amended values for log K and log K* (bolded) of Cu(II) complexes with NSFRY-NH_2 and its analogues from Janicka-Klos et al. (5) and their $^3\chi^v$ index*

Peptide	Species	Coordination mode	log *β*	log *K*	log *K**	$^3\chi^v$
NSFRY-NH_2 (**1**)	$[CuLH]^{2+}$	1N	14.13	4.98	**-1.89**	8.901
	$[CuL]^{+}$	2N	9.15	6.44	**-6.87**	9.773
	$[CuLH_{-1}]$	3N	2.71	6.73	**-13.31**	11.218
	$[CuLH_{-2}]^{-}$	4N	-4.02	9.48	**-20.04**	12.596
ASFRY-NH_2 (**2**)	$[CuLH]^{2+}$	1N	14.05	4.90	**-3.25**	8.678
	$[CuL]^{+}$	2N	9.15	7.29	**-8.15**	9.545
	$[CuLH_{-1}]$	3N	1.86	5.97	**-15.44**	10.991
	$[CuLH_{-2}]^{-}$	4N	-4.11	10.49	**-21.41**	12.369
(*R*)-ASFRY-NH_2 (**3**)	$[CuLH]^{2+}$	1N	15.88	5.16	-1.49	8.678
	$[CuL]^{+}$	2N	10.72	5.64	-6.65	9.545
	$[CuLH_{-1}]$	3N	5.08	6.80	-12.29	10.991
	$[CuLH_{-2}]^{-}$	4N	-1.72	6.43	-19.09	12.369
NAFRY-NH_2 (**4**)	$[CuLH]^{2+}$	1N	13.8	5.17	**-2.31**	8.837
	$[CuL]^{+}$	2N	8.63	6.84	**-7.48**	9.809
	$[CuLH_{-1}]$	3N	1.79	6.35	**-14.32**	11.25
	$[CuLH_{-2}]^{-}$	4N	-4.56	10.26	**-20.67**	12.627
NShFRY-NH_2 (**5**)	$[CuLH]^{2+}$	1N	13.45	**4.59**	-2.6	9.182
	$[CuL]^{+}$	2N	8.86	**7.26**	-7.19	10.055
	$[CuLH_{-1}]$	3N	1.60	**6.28**	-14.45	11.496
	$[CuLH_{-2}]^{-}$	4N	-4.68	**10.33**	-20.73	12.873
NSARY-NH_2 (**6**)	$[CuLH]^{2+}$	1N	13.98	4.90	**-1.92**	7.737
	$[CuL]^{+}$	2N	9.08	6.96	**-6.82**	8.609
	$[CuLH_{-1}]$	3N	2.12	6.63	**-13.78**	10.155
	$[CuLH_{-2}]^{-}$	4N	-4.51	10.54	**-20.41**	11.528
NSFAY-NH_2 (**7**)	$[CuLH]^{2+}$	1N	14.22	4.91	**-2.10**	8.035
	$[CuL]^{+}$	2N	9.31	7.07	**-7.01**	8.907
	$[CuLH_{-1}]$	3N	2.24	6.57	**-14.08**	10.352
	$[CuLH_{-2}]^{-}$	4N	-4.33	10.69	**-20.65**	11.835
NSFRA-NH_2 (**8**)	$[CuL]^{2+}$	1N	3.74	4.72	**-2.57**	7.65
	$[CuLH_{-1}]^{+}$	2N	-0.98	7.08	**-7.29**	8.522
	$[CuLH_{-2}]$	3N	-8.06	7.14	**-14.37**	9.968
	$[CuLH_{-3}]^{-}$	4N	-15.2		**-21.51**	11.346
NSAAA-NH_2 (**9**)	$[CuL]^{2+}$	1N	3.87	4.33	-2.73	5.62
	$[CuLH_{-1}]^{+}$	2N	-0.46	7.11	-7.06	6.493
	$[CuLH_{-2}]$	3N	-7.57	7.70	-14.17	8.039
	$[CuLH_{-3}]^{-}$	4N	-15.27	8.63	-21.87	9.517
NSFAA-NH_2 (**10**)	$[CuL]^{2+}$	1N	3.90	**4.54**	-2.63	6.784
	$[CuLH_{-1}]^{+}$	2N	-0.64	7.08	-7.17	7.656
	$[CuLH_{-2}]$	3N	-7.72	7.34	-14.25	9.102
	$[CuLH_{-3}]^{-}$	4N	-15.06	8.64	-21.59	10.584
NSARA-NH_2 (**11**)	$[CuL]^{2+}$	1N	3.93	4.58	-2.57	6.486
	$[CuLH_{-1}]^{+}$	2N	-0.65	7.2	-7.15	7.359
	$[CuLH_{-2}]$	3N	-7.85	7.33	-14.35	8.904
	$[CuLH_{-3}]^{-}$	4N	-15.18	9.02	-21.68	10.278
NSAAY-NH_2 (**12**)	$[CuLH]^{2+}$	1N	13.80	4.8	-2.41	6.871
	$[CuL]^{+}$	2N	9.00	7.27	-7.21	7.743
	$[CuLH_{-1}]$	3N	1.73	6.72	-14.48	9.289
	$[CuLH_{-2}]^{-}$	4N	-4.99	10.25	-21.2	10.767
AAAAA-NH_2 (**13**)	$[CuL]^{2+}$	1N	4.56	5.13	-3.28	5.334
	$[CuLH_{-1}]^{+}$	2N	-0.57	7.50	-8.41	6.301
	$[CuLH_{-2}]$	3N	-8.07	8.33	-15.91	7.842
	$[CuLH_{-3}]^{-}$	4N	-16.4		-24.24	9.32

Table 2 *Regression models for the estimation of log β for Cu(II) complexes with NSFRY-NH$_2$ and its analogues*

Eq.	*N*	Peptides	Regression coefficients				*r*	S.E.	S.E.$_{cv}$
			a_1 (S.E.)	a_2 (S.E.)	a_3 (S.E.)	*b* (S.E.)			
5	28	with Tyr	-4.849(49)	4.75(10)		14.47(78)	0.999	0.35	0.39
5	20	without Tyr	-5.030(41)	4.728(83)		5.90(48)	0.999	0.25	0.30
6	48	all	-4.926(36)	4.733(75)	10.35(17)	5.02(44)	0.999	0.35	0.38
6	36	without CuP$^-$	-4.979(54)	4.780(85)	10.14(17)	5.22(44)	0.999	0.30	0.34

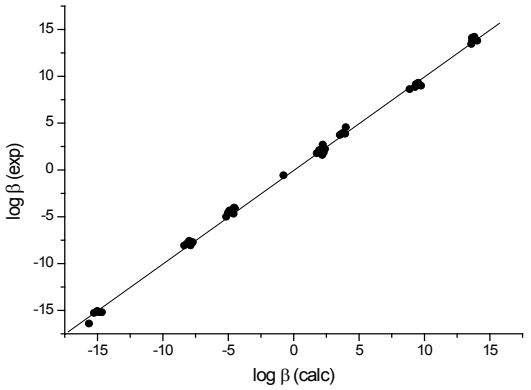

Figure 3 *Experimental* vs. *calculated values of log β for complexes of Cu(II) complexes with NSFRY-NH$_2$ and its analogues (*N*=48, Table 2) using Equation 6*

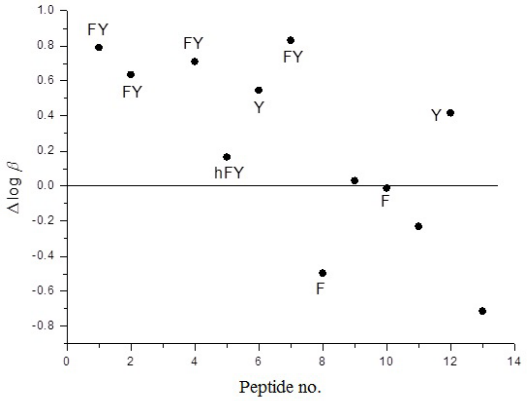

Figure 4 *Residual plot of log β values of CuP$^-$ (test set,* N*=12) calculated from the regression model parameterised on all other complexes (training set,* N*=36; Table 2) using Equation 6. F, hF, and Y denote complexes of peptides with respective residues*

As the slopes for complexes with different peptides are almost the same – from -4.64 to -4.92 and from -4.88 to -5.21, for Subset 1 and 2, respectively – we used a single model to estimate all log *β*s in a subset:

$$\log \beta = a_1[^3\chi^v(\mathrm{CuP})^n] + a_2[^3\chi^v(\mathrm{CuP})^{2+}] + b \qquad [5]$$

The variable $^3\chi^v(\mathrm{CuP})^{2+}$, *i.e.* the $^3\chi^v$ of a peptide complex in its fully protonated form, was added to Equation 4 because it determines the distances between the regression lines for the complexes of each peptide (Figure 2).

The model yielded S.E.$_{cv}$=0.39 and S.E.$_{cv}$=0.30 for Subset 1 and 2, respectively (Table 2). From Subset 1 we omitted complexes with the (*R*)-alanine residue [(*R*)-ASFRY-NH$_2$] because it is the only residue with unnatural configuration and the model gave much worse results with those complexes: *r*=0.993 and S.E.$_{cv}$=0.89 (*N*=32).

As there was no significant difference between regression parameters for the two subsets (Table 2) except in their intercepts (*b*), we developed a model that included both subsets (*N*=48) by introducing an indicator (dummy) variable (*In*=1 and *In*=0, for Subsets 1 and 2, respectively) to Equation 5:

$$\log \beta = a_1[^3\chi^v(\mathrm{CuP})^n] + a_2[^3\chi^v(\mathrm{CuP})^{2+}] + a_3 In + b \qquad [6]$$

The model yielded *r*=0.999 and S.E.$_{cv}$=0.38 (Table 2, Figure 3). This is worse than the previous model for Subset 2, but slightly better than for Subset 1.

In order to investigate additional stabilisation of CuP$^-$ (4N) complexes with tyrosine and phenylalanine residue (Y and F) caused by metal-π interactions (5), we calculated log *β* values of CuP$^-$ (test set, *N*=12) from the model parameterised on all other complexes (training set, *N*=36) using Equation 6 (Table 2). Differences between experimental and calculated log *β* values show that residuals for the CuP$^-$ complexes with tyrosine peptides differ significantly from others (Figure 4), as all calculated values for log *β* of complexes belonging to Subset 1 are lower than the experimental ones, whereas values calculated for Subset 2 are higher than the experimental, except for NSAAA-NH$_2$. Furthermore, the S.E. of the predicted log *β* for tyrosine peptide complexes was twice as high as the S.E. for other complexes (0.59 *vs.* 0.28).

As our model cannot explicitly calculate electronic interactions, systematically lower and poorer (S.E.=0.59) predicted stabilities for complexes that are capable of aromatic stabilisation may also evidence additional stabilisation of CuP$^-$ complexes. In addition, of all 4N-complexes with tyrosine peptides, error was the smallest for NShFRY-NH$_2$ (hFY, Figure 4), which is in accordance with the report by Janicka-Klos et al. (5), suggesting that π-interactions with Cu(II) are less favourable for stability due to the elongation of phenylalanine side chain. However, peptides with phenylalanine residue (F, Figure 4) do not differ from other non-tyrosinic peptides, indicating that phenylalanine residue does not participate in cation-π interactions, but seems to enhance tyrosine interactions.

Finally, we would like to say a few words about the possible influence of Cu(II) on ANF function. Even though NSFRY-NH2 (1) showed very high affinity to Cu(II), it did not have the highest stability constants among the modelled pentapeptides (Table 1). It is therefore possible that Cu(II) binding to the C-terminal sequence of ANF is influenced by the neighbouring disulphide loop and we believe that the graph theory method may help to prove or disprove this hypothesis.

Acknowledgement

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Modeliranje vezivanja bakra(II) za pentapeptide povezane s atrijalnim natriuretičkim faktorom pomoću indeksa povezanosti $^3\chi^v$

Služeći se teorijom molekularnih grafova istraživali smo vezivanje NSFRY-NH_2 i 12 srodnih pentapetidnih amida za Cu(II) kao modelnog sustava za interakciju bakra s peptidnom molekulom atrijalnog natriuretičkog faktora (ANF). Modeli linarne regresije temeljeni na valencijskom indeksu povezanosti trećega reda ($^3\chi^v$) reproducirali su eksperimentalnu konstantu stabilnosti (log β) za komplekse koordinacije 1N, 2N, 3N i 4N sa standardnom pogreškom u rasponu od 0,30 do 0,39 log β jedinica. Razvili smo odvojene modele za sedam tirozinskih (N=28) i pet netirozinskih (N=20) peptida te skupni model s indikatorskom varijablom za obje vrste peptida (N=48). Rezultati upućuju na dodatnu aromatsku stabilizaciju u kompleksima vrste 4N zbog interakcija kationa s π-orbitalama tirozinskog ostatka, ali ne i fenilalaninskoga. Ispravili smo i pogrešne vrijednosti log K i log K* nastale omaškom u radu Anne Janicka-Klos i sur. 2013.

KLJUČNE RIJEČI: *kompleksni spojevi; peptidi; konstante stabilnosti; topološki indeksi*