

Estimation of Stability Constants of Copper(II) and Nickel(II) Chelates with 1,2-Diaminoethanes by the Overlapping Spheres Method*

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The method of overlapping spheres (OS) was applied to the estimation of stability constants ($\log K_1$) of copper(II) and nickel(II) *mono*-complexes with 1,2-diaminoethane and its *N*-alkylated, *N,N*-dialkylated, and *C*-substituted derivatives. The central sphere, with radius 3 or 4 Å, was situated at the central atom, or in the equatorial (N1 or N2) or apical position (X1 or X2). The overlapping volumes of the central sphere and the van der Waals spheres of the surrounding atoms were calculated, and correlated with the stability constants measured at two temperatures, 0 and 25 °C. The regression analysis included the training set consisting of 14 ligands, subsequently divided into three subsets (classes), consisting of 5, 5, and 4 ligands. The general multivariate model including all the experimental data, *i.e.*, $\log K_1$ for Cu^{II} and Ni^{II} complexes measured at 0 and 25 °C ($N = 56$), was developed by introducing two indicator variables. Predictive power of the best models was tested on stability constants of five copper(II) diamine chelates with highly variable structures, yielding the reproduction of experimental data with an error of 0.02–0.75 ($rms = 0.34$) $\log K$ units.

INTRODUCTION

The method of overlapping spheres (OS) encompasses any method based on the calculation of the overlapping volume, or any similar quantity, of the spheres centred on atoms or any well-defined position of a molecule. The method was initially employed for calculations of the solvation (hydration) energy of proteins (hydration shell model);^{1–5} it was subsequently applied in 3D-QSAR analysis and drug design,^{6–8} in the construction of molecular geometry from the connectivity matrix,^{9–11} and in the search for low-energy conformations.^{12–16} In the last mentioned application, the centre of the sphere is not situated at any atom, but at the geometrical centre of the molecule¹² or molecular fragment defined by molecular topology^{13–15} or atom clusters.¹⁶

Our first applications of the OS method for the estimation of stability constants of coordination compounds were directed to the classical problem in coordination chemistry, *i.e.*, estimation of the diastereoselectivity and enantioselectivity effects in the complexes of amino acids and their derivatives.^{17–22} A model for estimation of the enantioselectivity effect was developed for copper(II) chelates with *N*-alkylated and *N,N*-dialkylated amino acids,²³ which yielded results comparable with those obtained by molecular-mechanics calculations.²⁴ In our last paper,²⁵ the stability constants of *mono*- and *bis*-chelates of copper(II) with naturally occurring amino acids and *N*-alkylated and *N,N*-dialkylated glycines were reproduced with an error of 0.1–0.5 $\log K$ units. But, our interest is not restricted to a particular method or class of

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compounds; the general aim of our research is development of a general model (or set of models) for estimation of stability constants, by using the OS method and topological indices^{26–28} alike.

In this paper, we focus our attention on the complexes of 1,2-diaminoethane (ethylenediamine) and its derivatives. Needless to say, these substances are among the best studied coordination compounds. For instance, the first conformational analysis²⁹ and molecular-mechanics calculations^{30–32} on coordination compounds were performed on cobalt(III) diamines. Moreover, derivatives of 1,2-diaminoethane were investigated to study the diastereoselectivity in metal complexes,³³ and many diamines and polyamines have found wide application in analytical chemistry.³⁴ In this paper, however, we restrict our interest to *mono*-complexes with a five-membered chelate ring, but – in contrast to our previous paper²⁵ – we studied also nickel(II) complexes, not only the copper(II) ones, and made correlations for stability constants measured at two temperatures.

METHODS

The overlapping spheres (OS) approach is based on the evaluation of the function:³⁵

$$V^* = \sum V_j(S_v \cap s_j), \quad (1)$$

where V^* is the overlapping volume of the central sphere S_v (with radius R_v) and volumes of van der Waals spheres s_j of the surrounding atoms (the details of calculations along with the set of van der Waals radii are given elsewhere¹³). The central sphere is situated at the central atom ($M = \text{Cu}, \text{Ni}$) or at an atom in the first coordination sphere ($\text{N1}, \text{N2}, \text{X1}$ or X2), Figure 1. Letter X marks two apically situated »dummy» atoms ($M\text{-X} = 2.5 \text{ \AA}$). The overlapping volume of the central sphere and the atom at

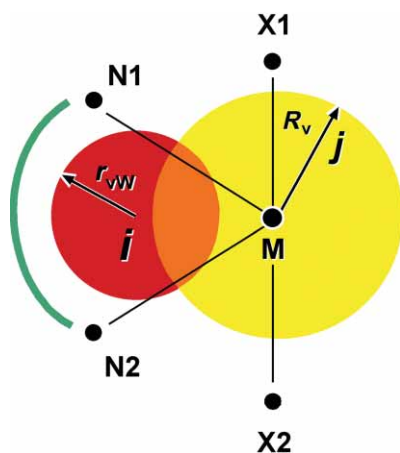


Figure 1. General scheme of the overlapping spheres (OS) model. The j -th central sphere, with radius R_v , is situated at the central atom (M). It overlaps with the van der Waals sphere, with the radius r_{vw} , of the i -th atom.

which it was situated was not taken into account in the calculations.

For the regression analysis, we used V^* (Eq. (1)) as well as its two composite functions. The first is the mean of the overlapping volumes of the spheres situated at N different atoms, A_i :

$$Os_1(\{A\}) = 1/N \sum V^*(A_i) \quad (2)$$

The second function was introduced in our previous paper²⁵ to cope with the apically positioned atoms:

$$Os_2(A_1, A_2) = [V^{*2}(A_1) + V^{*2}(A_2)] [V^*(A_1) + V^*(A_2)]^{-1} \quad (3)$$

Calculation of the overlapping volume of the central sphere and the surrounding atoms (Eq. (1)) was performed by the separate FORTRAN program, and all the regression calculations were done using the CROMRsel procedure.³⁶ All molecular mechanics calculations, needed to find the chelate conformers, were done with the program developed by Kj. Rasmussen and co-workers,^{37–39} using the force field denoted as FF3a,^{40,41} developed for copper(II) complexes. For nickel(II) complexes, we used the same force field, FF3a, since the force field modified for nickel ($\text{Ni-N} = 2.1 \text{ \AA}$, $\text{Ni-X} = 2.2 \text{ \AA}$) yielded virtually the same results as the original force field ($\text{Cu-N} = 2 \text{ \AA}$, $\text{Cu-X} = 2.5 \text{ \AA}$).

RESULTS AND DISCUSSION

The basic training set consisted of 14 *mono*-complexes of 1,2-diaminoethane (**1**) and its five N -monosubstituted (**2–6**), four N,N' -bisubstituted (**7–10**), and four (**11–14**) C -substituted derivatives (Table I). For all ligands, the first stability constants, $\log K_1$ ($\log \beta_{110}$), were taken from the literature. All $\log K_1$ values were measured at $I = 0.5 \text{ mol L}^{-1}$, at two temperatures, 0 and 25°C , and for two metals, copper(II) and nickel(II).

For further calculations, the conformation (or configuration) with the lowest OS volume for each centre was chosen for every complex, and the remaining structures were not taken into account. As the Os_2 function (Eq. (3)) proved better than the Os_1 function (Eq. (2)) for calculating the influence of N or X centres, we only refer to the values obtained by the former formula (Tables I, II, Supplement and Figure 2). These findings are concordant with the results presented in our previous paper: overlapping volumes averaged for all molecular conformations yielded poor agreement with the experiment, and the Os_1 function proved inferior to the Os_2 function.²⁵

Agreement between the measured and estimated values for complexes of both metals is virtually the same, $\langle r \rangle = 0.782$ for Cu^{II} and $\langle r \rangle = 0.785$ for Ni^{II} . The estimates for $T = 298 \text{ K}$ ($\langle r \rangle = 0.842$) are, however, substantially better than the estimates for $T = 273 \text{ K}$ ($\langle r \rangle =$

TABLE I. Mono-complexes of 1,2-diaminoethane and its derivatives

No.	Ligand	Configuration, conformation	log $K_1(\text{Cu})$ $T = 273 \text{ K}$	log $K_1(\text{Cu})$ $T = 298 \text{ K}$	log $K_1(\text{Ni})$ $T = 273 \text{ K}$	log $K_1(\text{Ni})$ $T = 298 \text{ K}$	Reference
1	1,2-diaminoethane	–	11.34	10.76	7.92	7.60	44
2	<i>N</i> -methyl-1,2-diaminoethane	<i>e</i>	11.12	10.55	7.95	7.36	44
3	<i>N</i> -ethyl-1,2-diaminoethane	<i>e(t)</i>	10.55	10.19	7.19	6.78	44
4	<i>N</i> -propyl-1,2-diaminoethane	<i>e(tt)</i>	10.49	9.98	7.10	6.60	44
5	<i>N</i> -butyl-1,2-diaminoethane	<i>e(ttt)</i>	10.47	9.94	7.25	6.73	44
6	<i>N</i> -isopropyl-1,2-diaminoethane	<i>e(R)g⁻, e(R)g^(a)</i>	9.46	9.07	5.62	5.17	44
7	<i>N,N'</i> -dimethyl-1,2-diaminoethane	<i>e(S), e(S)</i>	11.22	10.47	7.87	7.11	45
8	<i>N,N'</i> -diethyl-1,2-diaminoethane	<i>e(S)t, e(S)t</i>	10.84	9.30	7.42	5.62	45
9	<i>N,N'</i> -dipropyl-1,2-diaminoethane	<i>e(S)tt, e(S)tt</i>	9.39	8.79	5.87	5.52	45
10	<i>N,N'</i> -dibutyl-1,2-diaminoethane	<i>e(S)ttt, e(S)ttt</i>	9.44	8.67	6.03	5.42	45
11	1,2-diaminopropane	<i>e</i>	11.65	10.78	8.05	7.43	46
12	(<i>R,S</i>)-2,3-diaminobutane	<i>e(R), a(S)</i>	11.50	10.72	7.37	7.04	46
13	(<i>R,R</i>)-2,3-diaminobutane	<i>e(R), e(R)</i>	12.22	11.39	8.30	7.71	46
14	2-methyl-1,2-diaminopropane	–	11.31	10.53	7.27	6.77	46
15	<i>N</i> -isopropyl-2-methyl-1,2-propanediamine	<i>e(R)g⁻</i>		9.03			47
16	<i>N,N</i> -diethyl-1,2-diaminoethane	<i>e(t), e(t)</i>		8.17			48
17	<i>N,N,N',N'</i> -tetramethyl-1,2-diaminoethane	–		7.38			49
18	<i>cis</i> -1,2-diaminocyclohexane	–		10.61			50
19	<i>trans</i> -1,2-diaminocyclohexane	–		10.94			50

(a) Critical torsion angle is defined as M-N-C-H; the first conformation was used in calculation of models with M and N, and the second one for calculation of models with X.

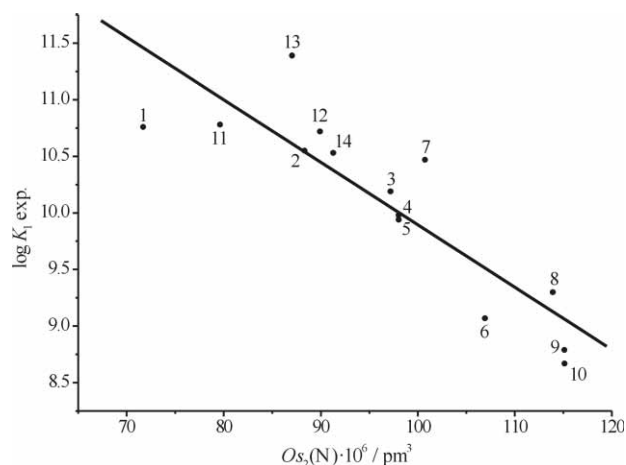


Figure 2. Univariate linear regression of $\log K_1(\text{Cu})$, measured at $T = 298 \text{ K}$, on $\text{Os}_2(\text{N})$ function. $R_v = 3 \text{ \AA}$ (Table I, Supplement).

0.720). Such a difference could hardly be attributed to the imprecision or systematic error of the OS method; it would rather be found in the poor quality of measurements at $T = 273 \text{ K}$.

Position at the central atom (M) generally yielded the most consistent results (e.g., $r = 0.835\text{--}0.861$, $T = 298 \text{ K}$), but not substantially better than the other central sphere positions (e.g., $r = 0.809\text{--}0.891$, $\text{Os}_2(\text{N})$, $T = 298 \text{ K}$). Averaged values, $\text{Os}_1(\text{M}, \text{X}, \text{N})$, did not generally yield better results, but – as may be expected – the results within the range of values obtained by calculations for separate centres. The sole exception is the regression for nickel complexes at $T = 298 \text{ K}$ ($R_v = 4 \text{ \AA}$), which yielded $r = 0.883$ ($r = 0.858\text{--}0.872$ for other regressions with the same parameters).

Calculated standard errors of estimate (S.E.) for $T = 298 \text{ K}$ are generally less than $0.5 \log K$ units (S.E. = $0.38\text{--}0.57 \log K$ units). The S.E. values for points deleted from the regression in the procedure of crossvalidation⁴² (leave-one-out) are close to these values (S.E._{cv} = $0.44\text{--}0.65 \log K$ units), showing the regression stability and suitability of the model for prediction of experimental data.

Improvement of the method was sought in a better grouping of data. The initial training set of 14 molecules was divided into three sets. The first set contained complexes of primary amines (**1**, **11–14**, Table I). In the second set were only secondary amines (**2–6**), and the third set contained complexes of disubstituted secondary amines (**7–10**). The results of such a grouping are highly variable. For copper(II) complexes with primary amines $r < 0.6$ for all regressions, but nickel(II) complexes in the same group gave $r = 0.487\text{--}0.947$ ($\langle r \rangle = 0.789$) and S.E. = $0.12\text{--}0.35 \log K$ units. The group of secondary amines gave equally good results for copper(II) ($r = 0.947\text{--}0.998$, $\langle r \rangle = 0.972$, S.E. = $0.04\text{--}0.17 \log K$ units) and nickel(II) complexes ($r = 0.912\text{--}0.994$, $\langle r \rangle = 0.972$, S.E. = 0.08--

$0.30 \log K$ units). Unfortunately, all the models are highly unreliable in terms of S.E._{cv}. In the third group, despite the fairly good results for copper ($r = 0.732\text{--}0.997$, $\langle r \rangle = 0.890$, S.E. = $0.05\text{--}0.56 \log K$ units) and nickel ($r = 0.745\text{--}0.999$, $\langle r \rangle = 0.903$, S.E. = $0.04\text{--}0.58 \log K$ units), S.E._{cv} reached the value of $16 \log K$ units for both classes of complexes.

Multiple Linear Regression

In order to develop a model capable of predicting the value of stability constants from a small number of experimental data, we added two indicator variables⁴³ to our models. The first variable, x_2 , is the indicator variable dependent on temperature ($x_2 = 0$ for $T = 298 \text{ K}$, $x_2 = 1$ for $T = 273 \text{ K}$), and the second one, x_3 , is the indicator variable dependent on the kind of central atom ($x_3 = 0$ for Cu, i.e. $x_3 = 1$ for Ni). Regressions of all experimental data ($N = 56$, Table III, Supplement) yielded slightly better and more stable results compared to the simple (univariate) linear regressions (Tables I and II, Supplement): S.E. = $0.47\text{--}0.61$ (comp. $0.38\text{--}0.67$) $\log K$ units, S.E._{cv} = $0.51\text{--}0.65$ (comp. $0.44\text{--}0.77$) $\log K$ units (Figure 3). The same holds true for regressions ($N = 28$, Table IV, Supplement) calculated only for the constants measured at $T = 298 \text{ K}$ (S.E. = $0.38\text{--}0.56$, S.E._{cv} = $0.45\text{--}0.62$; comp. S.E. = $0.38\text{--}0.57$, S.E._{cv} = $0.44\text{--}0.65$; all values are expressed in $\log K$ units).

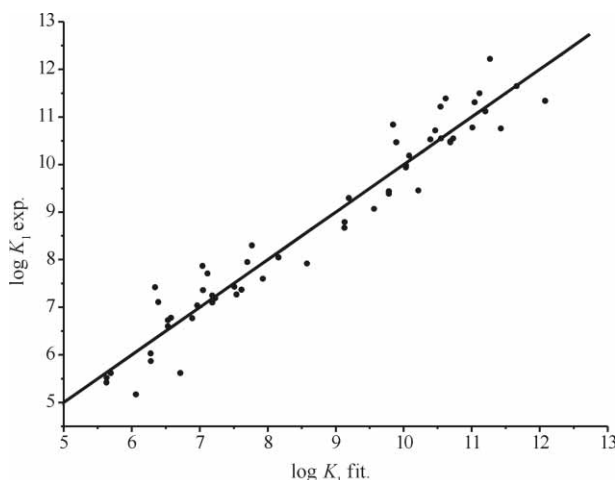


Figure 3. Plot of the experimental (measured) vs. theoretical (fit) values, obtained by the multiple linear regression of $\log K_1(\text{Cu})$ and $\log K_1(\text{Ni})$, measured at $T = 298 \text{ K}$ and $T = 273 \text{ K}$, on $\text{Os}_2(\text{N})$ ($R_v = 3 \text{ \AA}$), x_2 and x_3 , $N = 56$ (Table III, Supplement).

True improvement of the model was achieved when the three subsets were re-examined by multiple regression (Tables V–VII, Supplement). In contrast to univariate linear regressions, where paucity of data disabled any reasonable prediction, the set of primary amines ($N = 20$) gave S.E. = $0.26\text{--}0.34 \log K$ units and S.E._{cv} = $0.30\text{--}0.42 \log K$ units. This result is substantially better

TABLE II. Prediction of $\log K_1$ for nickel complexes measured at $T = 298$ K. Results of multiple regressions on $\text{Os}_1(\text{M}, \text{X}, \text{N})$ function at $R_v = 3 \text{ \AA}$ (a) and $R_v = 4 \text{ \AA}$ (b) and $\text{Os}_2(\text{N})$ at $R_v = 3 \text{ \AA}$ (c) were referred; $N = 44$.

Ligand	$\log K_1$ exp.	$\log K_1^{(a)}$	$\log K_1^{(b)}$	$\log K_1^{(c)}$
4	6.60	6.81	6.83	6.65
8	5.62	5.70	5.80	5.74
12	7.04	6.96	6.80	7.12

(a) $\log K_1 = 16.05(67) - 0.091(10) x_1 - 3.39(16) x_2 + 0.49(16) x_3$, $R = 0.964$.

(b) $\log K_1 = 15.45(56) - 0.0461(47) x_1 - 3.39(15) x_2 + 0.49(15) x_3$, $R = 0.968$.

(c) $\log K_1 = 15.67(55) - 0.0575(56) x_1 - 3.39(15) x_2 + 0.49(15) x_3$, $R = 0.970$.

than that obtained by univariate linear or other multiple regression models. Even better prediction was obtained by regressions on secondary amines, 0.15–0.26 and 0.20–0.34 $\log K$ units for S.E. and S.E._{cv}, respectively. However, such good agreement was not achieved for the group of disubstituted secondary amines, 0.29–0.42 and 0.37–0.53 $\log K$ units for S.E. and S.E._{cv}, respectively.

The predictive power of the method was tested on a simulated case when only three stability constants for nickel complexes at $T = 298$ K were known (**1**, **2**, **7**, Table I), and for the complexes of three ligands (**4**, **8**, **12**) the experimental data are altogether missing (Table II). Thus, the regressions were calculated on 44 points. The missing eight values for nickel complexes were calculated by subtraction of 3.24 $\log K$ units from copper(II) constants measured at $T = 298$ K (3.24 $\log K$ units is the mean difference for three known constants, as measured for copper and nickel complexes). Despite such crude approximations, a reasonably good agreement between theoretical and experimental values was obtained ($\log K_{1\text{theor.}} - \log K_{1\text{exp.}} = 0.05\text{--}0.24$).

Final Test for the Goodness of Estimate

As a final test for suitability of the OS method to predict stability constants of diamine chelates, we chose five copper(II) complexes with greater structural diversity than the molecules in the training set (Table I). Two of the complexes (**16** and **17**) have ternary nitrogen atoms, and **15** is highly sterically crowded. Two ligands, **18** and **19**, are isomers of the same cyclic amine, 1,2-diaminocyclohexane. Among the number of models derived from the training set, we chose the models with the lowest S.E._{cv} values. Our second choice were the models that generally showed the best results, *i.e.*, models with the central sphere centered at M ($R_v = 3.0 \text{ \AA}$).

Variation among the estimated (theoretical) $\log K_1$ values for complexes **15**–**19** is 0.01–0.86 $\log K$ units (Table III). However, the best agreement was obtained with metal-centered models ($rms = 0.34 \log K$ units, $N = 14$ and

28), which is substantially better than the results obtained by other models presented in Table III ($rms = 0.41\text{--}0.53 \log K$ units). An alternative method is to calculate the mean and median of all estimated values for a particular complex presented in Table III. Both procedures gave very close values of the estimate (**15**: 8.85, 8.86; **16**: 8.72, 8.73; **17**: 7.89, 7.95; **18**: 10.44, 10.59; **19**: 10.78, 10.86 $\log K$ units for the mean and median values, respectively). Despite slightly poorer results obtained by these methods ($rms = 0.36 \log K$ units), the calculated mean and median values gave less variable results (differences between measured and estimated values are 0.16–0.55, 0.02–0.57 and 0.02–0.75 $\log K$ units for the mean, median, and the $R_v(\text{M}) = 3 \text{ \AA}$ model, respectively).

Stability constants for all complexes were, however, not equally well reproduced. The experimental data for complexes **16** and **17** were reproduced with an error up to 0.85 $\log K$ units, in contrast to the isomers of 1,2-diaminocyclohexane, **18** and **19**, which were reproduced within 0.21 $\log K$ units. Such discrepancy should be attributed to the structural difference of complexes **16** and **17** from the molecules in the training set (disubstituted nitrogen atom).

TABLE III. Estimation of stability constants for five copper(II) complexes measured at $T = 298$ K

Comp.	Experimental $\log K_1$	N (Table, Suppl.)	Theoretical $\log K_1$	
			The best model with respect to S.E. _{cv}	The best model generally, $R_v(\text{M}) = 3 \text{ \AA}$
15	9.03(2) (8.99–9.06) ^(a)	14(I)	8.73	8.91
		56(III)	8.81	9.02
		28(IV)	8.69	8.91
16	8.17 ^(b)	14(I)	8.46	8.92
		56(III)	8.55	9.03
		28(IV)	8.42	8.92
17	7.376(1) ^(c)	14(I)	8.21	7.49
		56(III)	8.31	7.69
		28(IV)	8.16	7.48
18	10.61(2) ^(d)	14(I)	10.15	10.59
		56(III)	10.18	10.59
		28(IV)	10.15	10.59
		20(V)	10.62	10.68
19	10.94(2) ^(d)	14(I)	10.53	10.87
		56(III)	10.54	10.85
		28(IV)	10.54	10.87
		20(V)	11.07	10.94

(a) $I = 0.5$ (KCl) mol L^{−1}, seven independent titrations, Ref. 47

(b) $I = 0.1$ (KCl) mol L^{−1}, Ref. 48

(c) $I = 0.5$ (KNO₃) mol L^{−1}, Ref. 49

(d) $I = 0.1$ (KCl) mol L^{−1}, Ref. 50

In conclusion, it has to be stated that the simplest model ($R_v(M) = 3 \text{ \AA}$, $N = 14$) proved to be the best. When the homogeneity of data in the training set was secured ($N = 20$), reproduction even within the limits of experimental error was obtained (molecules **18** and **19**). However, estimation of stability constants from the mean and median of the values obtained by different models is recommended to reduce error in the cases of extreme structural diversity.

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SAŽETAK

Procjena konstanti stabilnosti bakrovih(II) i niklovih(II) kelata s 1,2-diaminoetanima metodom preklapanja kugli**Ante Miličević i Nenad Raos**

Primjenjena je metoda preklapanja kugli (*overlapping spheres*, OS) za procjenu konstanti stabilnosti ($\log K_1$) bakrovih(II) i niklovih(II) mono-kompleksa s 1,2-diaminoetanom i njegovim *N*-alikiliranim, *N,N*-dialkiliranim i *C*-supstituiranim derivatima. Središnja kugla, radijusa 3 ili 4 Å, smještena je na središnji atom ili pak u ekvatorijalni (N1 ili N2) ili apikalni položaj (X1, X2) koordinacijskoga poliedra. Izračunani volumen preklapanja središnje kugle i van der Waalsovih sfera okolnih atoma koreliran je s konstantama stabilnosti što su izmjerene pri dvije temperature, 0 i 25 °C. Regresijska analiza provedena je na temeljnom skupu od 14 liganada, koji je u daljnjoj analizi podijeljen na dva skupa od pet liganada, te jedan skup od četiri liganda. Razvijen je multivarijatni model s dvije indikatorske varijable koji je uključivao sve vrijednosti $\log K_1$ izmjerene za Cu^{II} i Ni^{II} pri obje temperature ($N = 56$). Na kraju smo iskušali moć predviđanja najboljih modela na konstantama stabilnosti pet bakrovih(II) diaminskih kelata vrlo raznolike strukture, reproducirajući eksperimentalne vrijednosti u rasponu 0.02–0.75 ($rms = 0.34$) $\log K$ jedinica.

SUPPLEMENT

Estimation of Stability Constants of Copper(II) and Nickel(II) Chelates with 1,2-Diaminoethanes by the Overlapping Spheres Method

TABLE I. Linear regressions of $\log K_1(\text{Cu})$ on the overlapping volume (V^*) and its functions. $N = 14$ (molecules **1–14**, Table I)

T / K	R_v / pm	Variable	Intercept (S.E.)	Slope (S.E.)	r	S.E.	S.E. _{cv}
273	300	$V^*(\text{M})$	17.2(16)	−0.090(22)	0.763	0.55	0.65
		$Os_2(\text{X})$	14.3(17)	−0.134(50)	0.612	0.67	0.77
		$Os_2(\text{N})$	15.7(12)	−0.051(12)	0.769	0.54	0.66
		$Os_1(\text{M,X,N})$	15.9(15)	−0.077(22)	0.713	0.59	0.70
	400	$V^*(\text{M})$	15.1(11)	−0.0333(84)	0.754	0.55	0.66
		$Os_2(\text{X})$	16.4(14)	−0.063(16)	0.759	0.55	0.65
		$Os_2(\text{N})$	14.8(12)	−0.0289(87)	0.692	0.61	0.72
		$Os_1(\text{M,X,N})$	15.4(13)	−0.040(11)	0.723	0.58	0.68
298	300	$V^*(\text{M})$	17.0(12)	−0.096(17)	0.858	0.41	0.49
		$Os_2(\text{X})$	15.1(15)	−0.148(43)	0.706	0.57	0.65
		$Os_2(\text{N})$	15.41(86)	−0.0552(88)	0.875	0.39	0.48
		$Os_1(\text{M,X,N})$	15.8(11)	−0.087(16)	0.844	0.43	0.50
	400	$V^*(\text{M})$	14.73(80)	−0.0361(62)	0.861	0.41	0.49
		$Os_2(\text{X})$	16.0(11)	−0.067(12)	0.850	0.42	0.50
		$Os_2(\text{N})$	14.54(95)	−0.0321(67)	0.809	0.47	0.57
		$Os_1(\text{M,X,N})$	15.22(92)	−0.0444(79)	0.851	0.42	0.50

TABLE II. Linear regressions of $\log K_1(\text{Ni})$ on the overlapping volume (V^*) and its functions. $N = 14$ (molecules **1–14**, Table I)

T / K	R_v / pm	Variable	Intercept (S.E.)	Slope (S.E.)	r	S.E.	S.E. _{cv}
273	300	$V^*(\text{M})$	12.7(17)	−0.076(24)	0.677	0.60	0.70
		$Os_2(\text{X})$	11.7(16)	−0.134(47)	0.633	0.63	0.71
		$Os_2(\text{N})$	11.8(12)	−0.047(12)	0.742	0.54	0.65
		$Os_1(\text{M,X,N})$	11.9(15)	−0.071(22)	0.681	0.59	0.69
	400	$V^*(\text{M})$	11.1(11)	−0.0297(87)	0.700	0.58	0.68
		$Os_2(\text{X})$	12.5(14)	−0.059(15)	0.747	0.54	0.63
		$Os_2(\text{N})$	11.5(10)	−0.0308(74)	0.768	0.52	0.62
		$Os_1(\text{M,X,N})$	11.8(12)	−0.039(10)	0.745	0.54	0.63
298	300	$V^*(\text{M})$	13.6(13)	−0.096(18)	0.835	0.46	0.53
		$Os_2(\text{X})$	12.0(14)	−0.160(42)	0.740	0.56	0.63
		$Os_2(\text{N})$	12.24(83)	−0.0580(85)	0.891	0.38	0.44
		$Os_1(\text{M,X,N})$	12.5(11)	−0.090(16)	0.847	0.44	0.49
	400	$V^*(\text{M})$	11.42(83)	−0.0371(64)	0.858	0.42	0.49
		$Os_2(\text{X})$	12.9(10)	−0.070(12)	0.868	0.41	0.47
		$Os_2(\text{N})$	11.60(81)	−0.0358(58)	0.872	0.41	0.48
		$Os_1(\text{M,X,N})$	12.14(86)	−0.0475(73)	0.883	0.39	0.45

TABLE III. Multiple regressions of $\log K_1$ on the overlapping volume (V^*) and its functions. $N = 56$ (molecules **1–14**, Table I)

R_v / pm	x_1	Intercept (S.E.)	Slope x_1 (S.E.)	Slope x_2 (S.E.)	Slope x_3 (S.E.)	R	S.E.	S.E. _{cv}
300	$V^*(M)$	16.55(72)	−0.0895(99)	−3.50(14)	0.65(14)	0.965	0.51	0.55
	$Os_2(X)$	14.97(76)	−0.144(22)	−3.50(17)	0.65(17)	0.951	0.61	0.65
	$Os_2(N)$	15.22(51)	−0.0529(52)	−3.50(13)	0.65(13)	0.971	0.47	0.51
	$Os_1(M,X,N)$	15.45(62)	−0.0813(93)	−3.50(14)	0.65(14)	0.964	0.52	0.56
400	$V^*(M)$	14.49(48)	−0.0340(36)	−3.50(14)	0.65(14)	0.967	0.50	0.54
	$Os_2(X)$	15.89(60)	−0.0648(66)	−3.50(14)	0.65(14)	0.969	0.49	0.52
	$Os_2(N)$	14.54(50)	−0.0319(35)	−3.50(14)	0.65(14)	0.966	0.51	0.55
	$Os_1(M,X,N)$	15.06(53)	−0.0427(45)	−3.50(14)	0.65(14)	0.968	0.49	0.53

TABLE IV. Multiple regressions of $\log K_1$ on the overlapping volume (V^*) and its functions for $T = 298$ K. $N = 28$ (molecules **1–14**, Table I)

R_v / pm	x_1	Intercept (S.E.)	Slope x_1 (S.E.)	Slope x_2 (S.E.)	R	S.E.	S.E. _{cv}
300	$V^*(M)$	16.99(88)	−0.096(12)	−3.45(17)	0.974	0.43	0.49
	$Os_2(X)$	15.3(10)	−0.154(29)	−3.45(22)	0.956	0.56	0.62
	$Os_2(N)$	15.55(59)	−0.0566(60)	−3.45(15)	0.980	0.38	0.43
	$Os_1(M,X,N)$	15.89(74)	−0.089(11)	−3.45(17)	0.974	0.43	0.48
400	$V^*(M)$	14.80(57)	−0.0366(44)	−3.45(17)	0.976	0.42	0.47
	$Os_2(X)$	16.20(74)	−0.0686(82)	−3.45(17)	0.976	0.42	0.47
	$Os_2(N)$	14.79(62)	−0.0339(44)	−3.45(18)	0.973	0.44	0.50
	$Os_1(M,X,N)$	15.41(62)	−0.0459(53)	−3.45(16)	0.977	0.41	0.45

TABLE V. Multiple regressions of $\log K_1$ on the overlapping volume (V^*) and its functions for primary amines. $N = 20$ (molecules **1, 11–14**, Table I)

R_v / pm	x_1	Intercept (S.E.)	Slope x_1 (S.E.)	Slope x_2 (S.E.)	Slope x_3 (S.E.)	R	S.E.	S.E. _{cv}
300	$V^*(M)$	16.8(15)	−0.092(24)	−3.67(13)	0.62(13)	0.991	0.26	0.32
	$Os_2(X)$	12.76(44)	−0.060(14)	−3.67(12)	0.62(12)	0.992	0.24	0.30
	$Os_2(N)$	11.99(99)	−0.013(12)	−3.67(17)	0.62(17)	0.984	0.34	0.42
	$Os_1(M,X,N)$	13.0(10)	−0.036(17)	−3.67(16)	0.62(16)	0.986	0.31	0.39
400	$V^*(M)$	13.34(90)	−0.0223(82)	−3.67(15)	0.62(15)	0.988	0.29	0.36
	$Os_2(X)$	13.38(68)	−0.0311(84)	−3.67(13)	0.62(13)	0.991	0.26	0.32
	$Os_2(N)$	11.53(65)	−0.0049(51)	−3.67(17)	0.62(17)	0.984	0.34	0.42
	$Os_1(M,X,N)$	12.27(79)	−0.0131(75)	−3.67(16)	0.62(16)	0.985	0.32	0.40

TABLE VI. Multiple regressions of $\log K_1$ on the overlapping volume (V^*) and its functions for secondary amines. $N = 20$ (molecules **2–6**, Table I)

R_v / pm	x_1	Intercept (S.E.)	Slope x_1 (S.E.)	Slope x_2 (S.E.)	Slope x_3 (S.E.)	R	S.E.	S.E. _{cv}
300	$V^*(M)$	26.5(14)	−0.228(20)	−3.41(10)	0.48(10)	0.994	0.21	0.27
	$Os_2(X)$	32.5(16)	−0.672(48)	−3.407(88)	0.483(88)	0.995	0.18	0.23
	$Os_2(N)$	19.97(87)	−0.1026(88)	−3.41(10)	0.48(10)	0.994	0.21	0.28
	$Os_1(M,X,N)$	26.11(97)	−0.249(15)	−3.407(74)	0.483(74)	0.997	0.15	0.20
400	$V^*(M)$	19.88(73)	−0.0769(56)	−3.407(89)	0.483(89)	0.995	0.18	0.24
	$Os_2(X)$	22.12(77)	−0.1358(85)	−3.407(78)	0.483(78)	0.996	0.16	0.21
	$Os_2(N)$	16.32(72)	−0.0468(52)	−3.41(13)	0.48(13)	0.990	0.26	0.34
	$Os_1(M,X,N)$	19.77(58)	−0.0863(51)	−3.407(73)	0.483(73)	0.997	0.15	0.20

TABLE VII. Multiple regressions of $\log K_1$ on the overlapping volume (V^*) and its functions for disubstituted secondary amines. $N = 16$ (molecules **7–10**, Table I)

R_v / pm	x_1	Intercept (S.E.)	Slope x_1 (S.E.)	Slope x_2 (S.E.)	Slope x_3 (S.E.)	R	S.E.	S.E. _{cv}
300	$V^*(M)$	69(11)	−0.74(14)	−3.41(24)	0.90(24)	0.976	0.42	0.53
	$Os_2(X)$	76(12)	−1.77(33)	−3.41(24)	0.90(24)	0.976	0.42	0.53
	$Os_2(N)$	21.5(21)	−0.110(19)	−3.41(23)	0.90(23)	0.979	0.40	0.50
	$Os_1(M,X,N)$	27.6(32)	−0.241(42)	−3.41(23)	0.90(23)	0.978	0.40	0.50
400	$V^*(M)$	35.6(46)	−0.172(30)	−3.41(23)	0.90(23)	0.978	0.40	0.51
	$Os_2(X)$	39.3(36)	−0.297(35)	−3.41(17)	0.90(17)	0.988	0.29	0.37
	$Os_2(N)$	16.66(94)	−0.0462(58)	−3.41(18)	0.90(18)	0.987	0.31	0.39
	$Os_1(M,X,N)$	21.4(16)	−0.090(12)	−3.41(18)	0.90(18)	0.986	0.32	0.40