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Estimation of Stability Constants of Copper(II) Bis-chelates by the Overlapping Spheres Method

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The method of overlapping spheres (OS) was applied for the estimation of stability constants (β_2) of sets of (binary) copper(II) bis-complexes with 1,2-diaminoethanes (N = 14), aliphatic amino acids and their N-alkylated derivatives (N = 11), and naturally occurring amino acids (N = 9), along with a set of 16 mixed (ternary) copper(II) bis-complexes with naturally occurring amino acids. The central sphere, with the radius, R_v, 300 or 400 pm, was situated at the copper atom. The OS volumes (V^*) of the central sphere and the van der Waals spheres of the surrounding atoms were calculated from the structures of bis- or corresponding mono-complexes and correlated with the log β_2 values. Both approaches yielded similar results, differing in the reproduction of stability constants by less than 20 %. Bivariate linear regression was performed for mixed complexes, using ($V^*_1 + V^*_2$) and ($V^*_1 - V^*_2$) as independent variables (V^*_1 and V^*_2 correspond to the OS values for the two constituting chelate rings). The bivariate linear regression gave r = 0.961 and the reproduction of experimental data from 0.00 to 0.16 log β units (S.E.$_{cv}$ = 0.08 log β units).

Keywords
amino acids
1,2-diaminoethanes
molecular volumes

INTRODUCTION

Overlapping spheres (OS) is a vague term that covers all the methods based on the calculation of overlapping volumes of van der Waals radii of atoms and the sphere or spheres defined in a systematic way. The application of the method ranges from the calculation of hydration (solvation) energy of polymers[1–5] to the search for low-energy conformations,[6–10] construction of molecular connectivity (topology) from geometrical data,[11–13] and drug design.[14–16]

Stability of coordination compounds is due to many specific interactions (hydration, additional water coordination, steric strain, *etc.*). Many of these interactions are dependent on the OS volume, and therefore stability constants should be correlated with this quantity. But, in spite of such a vague underlying theoretical concept, the OS method gives fairly good estimates. The difference in energy between the enantiomeric conformers of copper(II) chelates with *N,N*-dialkylated amino acids estimated by the OS method differs by less than 5 kJ mol^{-1} from the energy calculated by more rigorous molecular mechanics calculations.[17] In our recent papers, we estimated the stability constants of copper(II) complexes with amino acids in an error range 0.1–0.5 log β units,[18] and stability constants of copper(II) and nickel(II) mono-

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complexes with diaminoethane and its derivatives within an error of 0.0–0.9 log β units.[19] These numbers are comparable with the results of topological analysis, which yielded an error of estimate usually less than 0.3 log β units.[20–22] When comparing the estimates, one has also to bear in mind that the measured stability constants for the same system differ typically by up to 0.3 log β units (*e.g.,* for copper complex with glycine log β_2 = 14.92–15.26 log β units, T = 298, I = 0.1 mol L^{-1}).[23]

In our previous papers we applied the OS method to estimate the stability constants of mono- or bis-complexes starting from the structures of their molecules. The task appears to be a very complex one because the overlapping spheres volume is determined by the molecular conformation. Moreover, in the case of bis-complexes, the problem of *cis/trans* isomerism appears, and the number of possible structures rises enormously (N conformations of a chelate ring give N (N+1) structures of the ML_2 complex). As previously,[19] we have taken into account only the structure with the minimal value of the OS volume for each molecule, but despite this simplification, the overlapping volume of a great number of isomers and conformers of the ML_2 complex has to be calculated. Faced with such complexity, we decided to develop a method capable of estimating stability constants of bis-complexes from the overlapping volumes of the constituting chelate rings (ML models). Also, to simplify the calculations, we calculated overlapping volumes placing the central sphere only at the central atom, and not also at the bite atoms like in our previous calculations.[18,19]

METHODS

The overlapping spheres (OS) approach is based on evaluation of the function:[23]

$$V^* = \Sigma\ V_j\ (S_v \cap s_j) \tag{1}$$

where V^* is the sum of overlapping volumes of the central sphere S_v and volumes of van der Waals spheres s_j of the neighboring atoms:[7,24]

$$V_j = 1/3\pi[2R_v^3 + 2r_j^3 + r_{vj}^3] - \pi[R_v^3 x^* + (r_{vj} - x^*)(r_j^2 + r_{vj} x^*)] \tag{2}$$

where

$$x^* = (R_v^2 - r_j^2 + r_{vj}^2)/r_{vj} \tag{3}$$

In Eqs. (2) and (3), r_j stands for the van der Waals radius of atom j penetrating the central sphere with radius R_v, and r_{vj} is the distance between the centers at atom j and the central sphere. Eq. (3) holds only for partial overlaps; otherwise V_j = 0 for $R_v + r_j = r_{vj}$, and V_j = 4/3 r_j^3 π for $r_j + r_{vj} = R_v$.

Central sphere is situated at the central atom (Figure 1). Set of the van der Waals radii is given elsewhere,[7] except r_j = 255 pm for sulphur.[24]

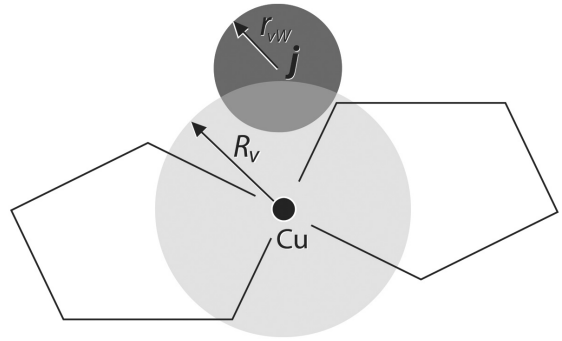

Figure 1. General scheme of the model of overlapping spheres (*cf.* Eq. 1).

Calculation of the overlapping volume (Eq. 1) was performed by a special FORTRAN program. All molecular-mechanics calculations, needed to find the conformers of copper(II) chelates, were done using the program developed by Kj. Rasmussen and co-workers.[25–27] Regression calculations, including the leave-one-out procedure of cross validation, cv, were done with the CROMRsel program.[28] The standard error of cross validation estimate is defined as:

$$S.E._{cv} = (\Sigma\ (\Delta X)^2/N)^{1/2} \tag{4}$$

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

RESULTS AND DISCUSSION

Complexes of 1,2-Diaminoethane and its Derivatives

As the first test of the reliability of the OS method for estimation of stability constants of bis-complexes we chose 1,2-diaminoethane and its derivatives using the same set of ligands as in the previous paper.[19] The set consists of 1,2-diaminoethane, its five *N*-alkylated and four *N,N´*-dialkylated derivatives, along with four C-substituted 1,2-diaminoethanes (Table I). All stability constants (β_2) were determined at the same temperature and ionic strength (T = 298 K, I = 0.5 mol L^{-1}).

In the models based on estimation of log β_2 from the OS volume of the whole molecule (models Nos. 2, 3, 5, and 6, Table I, Supplement), we constructed the geometry of complexes from the chelate ring conformations defined in Table I. As a bis-complex may appear as a *trans*- or *cis*-isomer, we tested two types of models. In

TABLE I. Stability constants (log β_2) of copper(II) bis-complexes with 1,2-diaminoethane and its derivatives

No.	Ligand	Configuration/Conformation	log β_2	Reference
1	1,2-diaminoethane	–	20.13	29
2	*N*-methyl-1,2-diaminoethane	e	19.11	29
3	*N*-ethyl-1,2-diaminoethane	*e*(t)	18.57	29
4	*N*-propyl-1,2-diaminoethane	*e*(tt)	18.14	29
5	*N*-butyl-1,2-diaminoethane	*e*(ttt)	18.21	29
6	*N*-isopropyl-1,2-diaminoethane	*e*(*R*)g^{-}[(a)]	16.52	29
7	*N*,*N*'-dimethyl-1,2-diaminoethane	*e*(*S*), *e*(*S*)	18.1	30
8	*N*,*N*'-diethyl-1,2-diaminoethane	*e*(*S*)t, *e*(*S*)t	15.62	30
9	*N*,*N*'-dipropyl-1,2-diaminoethane	*e*(*S*)tt, *e*(*S*)tt	14.34	30
10	*N*,*N*'-dibutyl-1,2-diaminoethane	*e*(*S*)ttt, *e*(*S*)ttt	13.51	30
11	1,2-diaminopropane	*e*	20.06	31
12	*(R,S)*-2,3-diaminobutane	*e*(*R*), *a*(*S*)	20.06	31
13	*(R,R)*-2,3-diaminobutane	*e*(*R*), *e*(*R*)	21.21	31
14	2-methyl-1,2-diaminopropane	–	19.58	31

[(a)] Critical torsion angle is defined as Cu-N-C-H.

the first type, only OS volumes of *trans*-isomers were taken into account; in the second type of models, the bis-complex with the minimal OS volume was selected among its *cis*- and *trans*-isomers. The models of the third type, where complexes appear as *cis*-isomers, were not tested because *cis*-configuration is not possible for all compounds.

The results of regression do not differ very much, irrespective of the model used. ML_2 models calculated at R_v = 300 pm (S.E.$_{cv}$ = 0.94–0.95 log β units, Nos. 2 and 3, Table I, Supplement, and Figure 2) appear to be

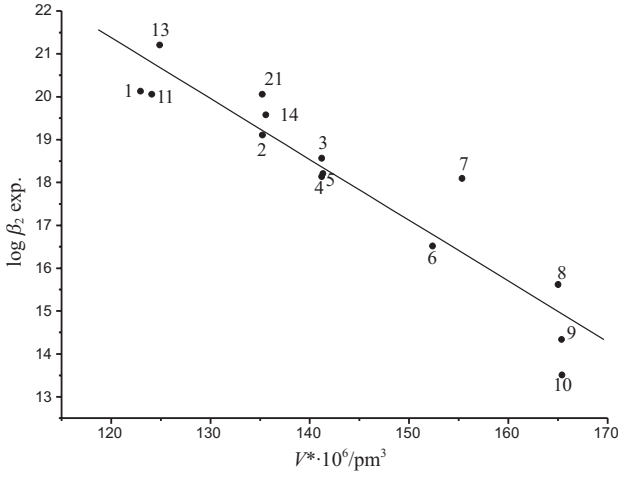

Figure 2. The best linear regression (3, Table I, Supplement) of log β_2 on the OS volume (V^*) for bis-complexes of 1,2-diaminoethane and its derivatives (N = 14, Intercept = 38.4(22), Slope = –0.142(15), r = 0.937, S.E. = 0.77, S.E.$_{cv}$ = 0.94). The numbering scheme corresponds to the notation in Table I.

superior to the other models (S.E.$_{cv}$ = 1.08–1.12 log β units). However, analysis of cv residuals for all the models shows virtually the same agreement between theory and experiment for ML (S.E.$_{cv}$ = 1.12 log β units) and ML_2 models (S.E.$_{cv}$ = 1.02 log β units; S.E.$_{cv}$ = 0.94–1.09). Despite the high estimation error, it has to be noted that the error is mainly due to complexes **7** and **10**; the log β_2 of *N*-alkylated 1,2-diaminoethanes (**2–6**) was reproduced with S.E.$_{cv}$ and the absolute error range of 0.27 (0.06–0.50), 0.19 (0.07–0.28), and 0.23 (0.01–0.29) log β units for the mean value of ML, ML_2, and both models, respectively (Table II, Supplement).

N-alkylated Glycines and Aliphatic Amino Acids

The second set for testing our method consisted of 11 bis-complexes of amino acids (Table II). It is the same set as in reference 18. All stability constants were determined at the same temperature and ionic strength (T = 298 K, I = 0.1 mol L^{-1}), with the exception for leucine (I = 0.01 mol L^{-1}). All ML_2 complexes were calculated as *trans*-isomers (Table III, Supplement).[18] The best results were obtained with the ML model No. 9, Figure 3 (S.E.$_{cv}$ = 0.50 log β units), but the difference from the worst model (No. 7, S.E.$_{cv}$ = 0.55 log β units) is rather small.

The S.E.$_{cv}$ and error ranges (Table IV, Supplement) for ML (S.E.$_{cv}$ = 0.52, range = 0.05–1.12 log β units) and ML_2 models (S.E.$_{cv}$ = 0.51, range = 0.06–0.93 log β units) are virtually the same. However, the main obstacle is the complex with *N*-iso-propylglycine; by discarding it, substantially better results were obtained (S.E.$_{cv}$ = 0.43, range = 0.01–0.70 log β units; calculated from the mean value of all regressions).

TABLE II. Stability constants (log β_2) of copper(II) bis-complexes with aliphatic amino acids and glycine derivatives

No.	Ligand	Conformation[(a)]	log β_2	Reference
1	Glycine	–	15.17	31
2	Alanine	*e*	14.82	32
3	Valine	*e*(g$^-$)	14.79	32
4	Leucine	*e*(gg)	14.34	33
5	*N*-Methylglycine	*e*	14.59	31
6	*N,N'*-Dimethylglycine	–	13.65	31
7	*N*-Ethylglycine	*a*(g$^-$)	13.55	31
8	*N,N'*-Diethylglycine	*a*(t) *e*(g$^-$)	12.86	31
9	*N*-Propylglycine	*a*(tg$^-$)	13.31	31
10	*N*-Butylglycine	*a*(g$^-$tg)	13.52	31
11	*N*-iso-Propylglycine	*a*(g)	12.45	31

*Torsion angles are defined for naturally occurring amino acids as N-C$^\alpha$-C$^\beta$-X, (X = C for Leu and X = H for Val) and for alkylated glycines as Cu-N-C-C, N-C-C-C and C-C-C-C, with the exception of iPr derivative (Cu-N-C-H).

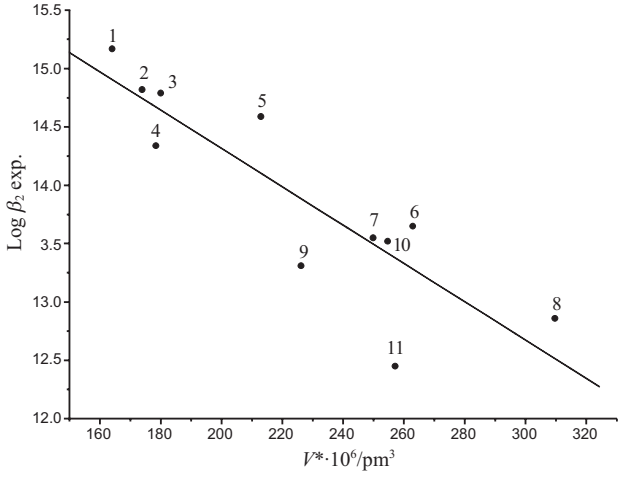

Figure 3. The best linear regression (9, Table III, Supplement) of log β_2 on the OS volume (V^*) for bis-complexes of aliphatic 0amino acids and their *N*-alkylated derivatives (N = 11, Intercept = 17.60(71), Slope = –0.0164(31), r = 0.869, S.E. =0.42, S.E.$_{cv}$ =0.50). The numbering scheme corresponds to the notation in Table II.

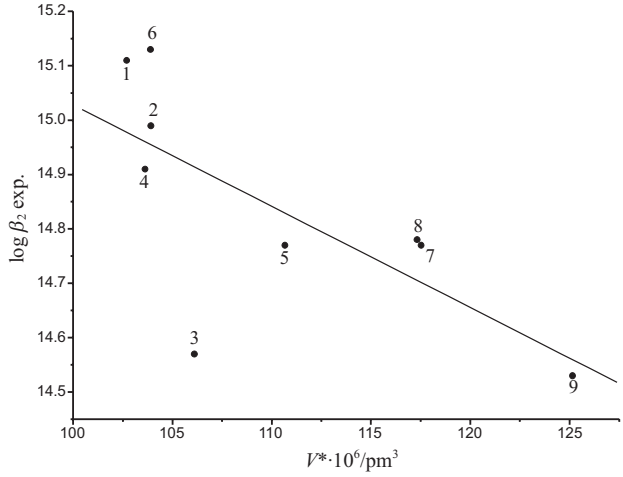

Figure 4. The best linear regression (12, Table V, Supplement) of log β_2 on the OS volume (V^*) for bis-complexes of naturally occurring amino acids (N = 9, Intercept = 16.89(78), Slope = –0.0186(71), r = 0.704, S.E. = 0.14, S.E.$_{cv}$ = 0.17). The numbering scheme corresponds to the notation in Table III.

Bis-complexes of Naturally Occurring Amino Acids

The third set of data for testing our model is a set coincident with the set used previously in order to estimate stability constants from topological indices.[21] The set consists of nine aliphatic, aromatic, and hydroxy amino acids (Table III), log β_2 values of which were measured at the same temperature and ionic strength (T = 298 K, I = 0.05 mol L^{-1}). All the models (Table V, Supplement) yielded results of virtually equal quality (S.E.$_{cv}$ = 0.17–0.19 log β units), but it has to be noted that the results are highly dependent on molecular conformation. Assuming all the chelate rings are in equatorial conformation (which has the lowest overlapping volume), a quite unrealistic regression was obtained (r = 0.825, but with a positive slope). Only when the conformation of one (*a/e*) or both (*a/a*) rings of aromatic and hydroxy amino acids was assumed, a realistic slope was obtained with a fair reproduction of experimental data (Figure 4). The rationale for the axial conformation for the chelate ring of aromatic and hydroxy amino acid is the assumption that in these complexes interactions between the side chain and the central atom occur, which in turn hinder the binding of the water molecule or the second ligand, leading to destabilization of the molecule.

Regressions presented in Table V (Supplement) yielded very similar residuals (Table VI, Supplement). They range from 0.04 to 0.24 log β units (absolute value), with the exception of molecule No. 3 (serine)

TABLE III. Stability constants (log β_2) of copper(II) bis-complexes with a representative set of amino acids

No.	Ligand	Conformation	log β_2	Reference
1	Glycine	–	15.11	34
2	Alanine	e	14.99	34
3	Serine	*e*(tg$^-$), *a*(gt)	14.57	34
4	Valine	*e*(g$^-$)	14.91	35
5	Threonine	*e*(g$^-$g$^-$), *a*(gt)	14.77	34
6	Leucine	*e*(gg)	15.13	36
7	Phenylalanine	*e*(tg), *a*(gg)	14.77	34
8	Tyrosine	*e*(tg), *a*(gg)	14.78	34
9	Methionine	*e*(ttt), *a*(ggg)	14.53	35

[(a)] Torsion angles are defined as N-C$^\alpha$-C$^\beta$-X, (X = C for Leu and X = H for Val); N-C$^\alpha$-C$^\beta$-O and C$^\alpha$-C$^\beta$-O-H for Ser and Thr; N-C$^\alpha$-C$^\beta$-C^1 and C$^\alpha$-C$^\beta$- C^1-C^2 for Phe and Tyr; N-C$^\alpha$-C$^\beta$-C, C$^\alpha$-C$^\beta$-C-S and C$^\beta$-C-S-C for Met.

with residuals from –0.36 to –0.40 log β units. Models based on the OS volume of one chelate ring (Nos. 11 and 13, Table V, Supplement) and the OS volume of bis-complex (Nos. 12 and 14, Table V, Supplement) yielded the same agreement with experimental data in terms of the overall cv parameters (S.E.$_{cv}$ = 0.18 log β units; mean residuals are from –0.36 to 0.22 and from –0.39 to 0.23 log β units for ML and ML_2 models, respectively). However, by refuting the serine complex, S.E.$_{cv}$ drops to 0.14 and 0.13 log β units for the mean values of ML and ML_2 models, respectively.

Estimation of the stability constants of mixed complexes in this series proved to be tedious (Table IV). Because of the enormous number of ring combinations in these chelates, estimation of the log β_2 values from the structure of ML_2 chelates appears to be quite impractical; we therefore solved the problem by using only models based on the calculation of the OS volumes of constituting chelate rings.

TABLE IV. Stability constants (log β_2) of copper(II) mixed bis-complexes with the set of amino acids defined in Table III

No.	Ligands (A, L)	log β_2[(a)]	Reference
1	Glycine, alanine	15.10	34
2	Glycine, serine	15.09	34
3	Glycine, threonine	15.13	34
4	Glycine, tyrosine	15.35	34
5	Glycine, phenylalanine	15.36	34
6	Alanine, serine	15.07	34
7	Alanine, threonine	15.08	34
8	Alanine, tyrosine	15.30	34
9	Alanine, phenylalanine	15.26	34
10	Valine, tyrosine	15.25	37
11	Serine, threonine	14.55	34
12	Serine, tyrosine	14.78	34
13	Serine, phenylalanine	14.77	34
14	Threonine, tyrosine	14.98	34
15	Threonine, phenylalanine	14.96	34
16	Tyrosine, phenylalanine	14.92	37

[(a)] log $\beta_2 \equiv$ log β_{CuAL} = log K_1 + log K_2 – log 2;
K_1 = [CuL] [Cu]$^{-1}$ [L]$^{-1}$, K_2 = [CuAL] [CuL]$^{-1}$ [A]$^{-1}$, Ref. 38.

Unfortunately, one-dimensional linear regression of the sum of the OS volumes of two chelate rings, $V_1^* + V_2^*$, yielded a very low regression coefficient and showed very distinct grouping of points (Figure 5). However, introduction of a new variable, $V_1^* - V_2^*$ ($V_1^* > V_2^*$), made it possible to make a correction for the asymmetric coordination. An estimate from the bivariate regression of log β_2 on ($V^*_1 + V^*_2$) and ($V^*_1 - V^*_2$) taking into account all the 16 complexes did not yield very satisfactory results (R = 0.650, S.E.$_{cv}$ = 0.345 for R_v = 400 pm). However, a close inspection of the data showed that the worst results were obtained for the mixed complex of both aromatic amino acids in the set, phenylalanine and tyrosine (residual = 0.28 log β units, cv residual = 1.18 log β unit). Discarding this point, fairly good results were ob-

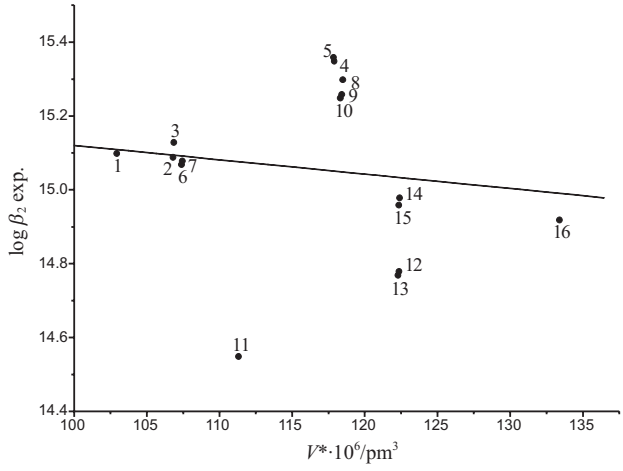

Figure 5. Linear regression of log β_2 on the OS volume (V^*) for mixed bis-complexes of naturally occurring amino acids (N = 16, Intercept = 15.51(86), Slope = –0.0039(74), r = 0.140). The numbering scheme corresponds to the notation in Table IV.

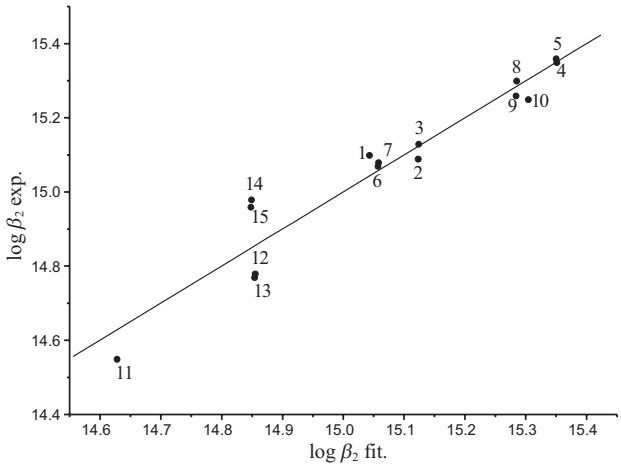

Figure 6. The best bivariate linear regression (15, Table VII, Supplement), experimental *vs.* calculated log β_2 values, for mixed bis-complexes of naturally occurring amino acids (N = 15, Intercept = 19.66(47), Slope ($V^*_1+V^*_2$) = –0.0452(44), Slope ($V^*_1–V^*_2$) = 0.0658(55), r = 0.961, S.E. = 0.06, S.E.$_{cv}$ = 0.08). The numbering scheme corresponds to the notation in Table IV.

tained (r = 0.961, S.E.$_{cv}$ = 0.08, Table VII, Supplement, Figure 6). The stability constants were reproduced very well for all the mixed complexes (Table VIII, Supplement). Residual values are in the absolute range of 0.00–0.16 (R_v = 300 pm), 0.01–0.20 (R_v = 400 pm), and 0.00–0.18 log β units (mean value of both sets). However, mixed complexes with aliphatic amino acids (**1**–**10**) yielded considerably lower residuals (0.00–0.07 log β units, absolute mean values for all models) compared to other chelates.

CONCLUSIONS

Taking into account all the results presented, it can be concluded that estimation of the stability constant of a bis-complex from its whole structure is not substantially better than its estimation from the structure of the corresponding ML complexes. Moreover, estimation of log β_2 for mixed complexes is practically possible only from the structures of ML complexes. Since ML_2 procedure is more demanding, we recommend the estimation of log β_2 from the overlapping volumes of mono-complexes.

As a general conclusion on the suitability of the OS method for the estimation of stability constants of bis-complexes, it has to be pointed out that the success is not so dependent on the type of the model used as on the set of the compounds used in regression. Results on the same set differ by less than 20 % in the S.E.$_{cv}$ value, but the S.E.$_{cv}$ values for all regressions and sets span the range from 0.08 to 1.12 log β units. (This span is about twice as large as the span for ML complexes,[18,19] but one has to bear in mind that log β_2's are twice as large as log β_1's.) Thus, a good choice of the training set is the first prerequisite for a successful application of the OS method for the estimation of stability constants of complex compounds.

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ABBREVIATIONS

M, metal (Cu);
ML, mono-complex;
ML_2, bis-complex;
β_1, stability constant of ML complex,
β_2, stability constant of ML_2 complex;
OS, overlapping spheres;
S.E., standard error;
S.E.$_{cv}$, standard error of cross validation;
a, axial conformation;
e, equatorial conformation.

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SAŽETAK

Procjena konstanta stabilnosti bis-kelata bakra(II) metodom preklapanja kugla

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Metodu preklapanja kugla (overlapping spheres, OS) primijenili smo za procjenu konstanta stabilnosti, β_2, skupova (binarnih) bakrovih(II) bis-kompleksa s 1,2-diaminoetanima (N = 14), alifatskim aminokiselinama i njihovim *N*-alkiliranim derivatima (N = 11), te prirodnim aminokiselinama (N = 9), zajedno sa skupom 16 miješanih (ternarnih) bakrovih(II) bis-kompleksa s prirodnim aminokiselinama. Središnja kugla, radijusa, R_v, 300 ili 400 pm, smještena je na bakrovom atomu. Izračunani volumeni preklapanja središnje kugle i van der Waalsovih sfera okolnih atoma iz struktura bis-kompleksa ili odgovarajućih mono-kompleksa korelirani su s vrijednostima log β_2. Oba su pristupa dala slične rezultate, razlikujući se u procjeni konstanti stabilnosti za manje od 20 %. Za miješane je komplekse provedena i bivarijatna linearna regresija, s ($V^*_1 + V^*_2$) i ($V^*_1 - V^*_2$) kao nezavisnim varijablama (V^*_1 i V^*_2 odgovaraju vrijednostima volumena OS za dva pripadna kelatna prstena). Bivarijatna linearna regresija dala je r = 0,961 i reproducirala eksperimentalne vrijednosti od 0,0 do 0,16 log β jedinica ($S.E._{cv}$ = 0,08 log β jedinica).

SUPPLEMENT

Estimation of Stability Constants of Copper(II) Bis-chelates by the Overlapping Spheres Method

TABLE I. Linear regressions of log β_2 on the overlapping volume (V^*); molecules **1**–**14**, Table I (Text)

Regression No.	R_v / pm	Variable	Intercept (S.E.)	Slope (S.E.)	r	S.E.	S.E.$_{cv}$
1	300	$2V^*(M)_{ML}$	38.3(27)	–0.141(19)	0.910	0.92	1.12
2		V^*(M) *trans*	38.6(22)	–0.143(16)	0.936	0.78	0.95
3		V^*(M) *cis/tr*	38.4(22)	–0.142(15)	0.937	0.77	0.94
4	400	$2V^*(M)_{ML}$	31.7(18)	–0.0528(69)	0.911	0.92	1.12
5		V^*(M) *trans*	31.7(17)	–0.0528(67)	0.916	0.89	1.09
6		V^*(M) *cis/tr*	31.7(17)	–0.0528(66)	0.917	0.88	1.08

TABLE II. Cross-validated residuals for all regression models referred to in Table I

Regression No.	1	2	3	4	5	6	Mean		
Molecule No.							ML models	ML_2 Models	All models
1	–1.19	–1.15	–1.05	–1.69	–1.67	–1.64	–1.44	–1.38	–1.40
2	0.66	0.43	–0.12	0.34	0.27	0.13	0.50	0.18	0.29
3	0.38	0.13	0.22	0.23	0.15	0.18	0.30	0.17	0.21
4	–0.08	–0.32	–0.25	–0.20	–0.28	–0.28	–0.14	–0.28	–0.23
5	0.00	–0.24	–0.15	–0.12	–0.21	–0.17	–0.06	–0.19	–0.15
6	0.09	–0.05	–0.29	0.15	0.11	–0.04	0.12	–0.07	–0.01
7	2.54	1.89	1.97	2.17	2.00	2.04	2.35	1.97	2.10
8	0.29	0.74	0.82	0.37	0.47	0.52	0.33	0.64	0.53
9	–1.28	–0.85	–0.79	–1.17	–1.06	–1.02	–1.22	–0.93	–1.03
10	–2.32	–1.93	–1.87	–2.22	–2.11	–2.08	–2.27	–2.00	–2.09
11	–1.05	–1.01	–0.92	–1.07	–1.05	–1.03	–1.06	–1.00	–1.02
12	0.72	0.90	0.92	1.05	1.12	1.13	0.88	1.02	0.97
13	0.53	0.56	0.64	0.92	0.94	0.96	0.72	0.78	0.76
14	0.24	0.43	0.45	0.56	0.64	0.64	0.40	0.54	0.49

TABLE III. Linear regressions of log β_2 on the overlapping volume (V^*); molecules **1**–**11**, Table II (Text)

Regression No.	R_v / pm	Variable	Intercept (S.E.)	Slope (S.E.)	r	S.E.	S.E.$_{cv}$
7	300	$2V^*(M)_{ML}$	18.9(11)	–0.0404(87)	0.840	0.46	0.55
8		V^*(M) *trans*	19.13(99)	–0.0426(80)	0.871	0.41	0.52
9	400	$2V^*(M)_{ML}$	17.60(71)	–0.0164(31)	0.869	0.42	0.50
10		V^*(M) *trans*	17.59(67)	–0.0164(29)	0.881	0.40	0.51

TABLE IV. Cross-validated residuals for all regression models referred to in Table III

Regression No.	7	8	9	10	Mean		
Molecule No.					ML models	ML_2 models	All models
1	0.54	0.52	0.36	0.35	0.45	0.44	0.44
2	0.15	0.14	0.09	0.10	0.12	0.12	0.12
3	0.09	0.09	0.18	0.18	0.14	0.13	0.13
4	–0.46	–0.47	–0.41	–0.32	–0.43	–0.4	–0.41
5	0.63	0.65	0.54	0.53	0.58	0.59	0.59
6	0.52	0.48	0.44	0.39	0.48	0.44	0.46
7	0.03	–0.07	0.06	–0.04	0.05	–0.06	–0.01
8	0.57	0.75	0.60	0.90	0.58	0.82	0.70
9	–0.63	–0.58	–0.63	–0.63	–0.63	–0.6	–0.62
10	0.00	–0.34	0.12	–0.08	0.06	–0.21	–0.08
11	–1.16	–0.87	–1.08	–0.98	–1.12	–0.93	–1.02

TABLE V. Linear regressions of log β_2 on the OS volume (V^*); molecules **1**–**9**, Table III (Text)

Regression No.	R_v/pm	Variable	Intercept (S.E.)	Slope (S.E.)	r	S.E.	$S.E._{cv}$
11	300	$2V^*(M)_{ML}$ *a/a*	15.86(39)	–0.0088(33)	0.707	0.14	0.17
12		V^*(M) tr *e/a*	16.89(78)	–0.0186(71)	0.704	0.14	0.17
13	400	$2V^*(M)_{ML}$ *a/a*	15.38(24)	–0.0025(11)	0.656	0.15	0.19
14		V^*(M) tr *e/a*	15.83(44)	–0.0050(22)	0.652	0.15	0.19

TABLE VI. Cross-validated residuals for the regression models referred to in Table V

Regression No.	11	12	13	14	Mean		
Molecule No.					ML models	ML_2 models	All models
1	0.18	0.17	0.17	0.15	0.17	0.16	0.17
2	0.04	0.04	0.04	0.04	0.04	0.04	0.04
3	–0.36	–0.40	–0.36	–0.39	–0.36	–0.39	–0.38
4	–0.06	–0.06	–0.04	–0.02	–0.05	–0.04	–0.05
5	–0.13	–0.07	–0.11	–0.09	–0.12	–0.08	–0.10
6	0.21	0.21	0.23	0.24	0.22	0.23	0.22
7	0.10	0.09	0.16	0.16	0.13	0.12	0.13
8	0.11	0.10	0.18	0.17	0.15	0.13	0.14
9	–0.06	–0.07	–0.19	–0.19	–0.13	–0.13	–0.13

TABLE VII. Bivariate linear regressions of log β_2 on the sum and the differences of the OS volumes $V^*(M)_{ML}$ and $V^*(M)_{MA}$ (V^*_1 and V^*_2); molecules **1**–**15**, Table IV (Text)

	R_v/pm	Intercept (S.E.)	$(V^*_1+V^*_2)$Slope (S.E.)	$(V^*_1-V^*_2)$Slope (S.E.)	r	S.E.	S.E.$_{cv}$
15	300	19.66(47)	–0.0452(44)	0.0658(55)	0.961	0.06	0.08
16	400	16.63(27)	–0.0098(15)	0.0153(19)	0.921	0.09	0.11

TABLE VIII. Cross-validated residuals for the regression models referred to in Table VII

Regression No.	15	16	Mean
Molecule No.			
1	0.08	0.07	0.07
2	–0.04	–0.05	–0.05
3	0.01	–0.02	–0.01
4	0.00	–0.06	–0.03
5	0.01	–0.04	–0.01
6	0.01	0.08	0.04
7	0.02	0.06	0.04
8	0.02	0.04	0.03
9	–0.03	–0.01	–0.02
10	–0.07	0.07	0.00
11	–0.13	–0.19	–0.16
12	–0.10	–0.17	–0.13
13	–0.11	–0.17	–0.14
14	0.16	0.20	0.18
15	0.14	0.18	0.16