CROATICA CHEMICA ACTA
CCACAA **78** (2) 175–180 (2005)

ISSN-0011-1643
CCA-2994
Original Scientific Paper

Estimation of Stability Constants of Copper(II) Chelates with Amino Acids by Overlapping Spheres Method*

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RECEIVED SEPTEMBER 7, 2004; REVISED JANUARY 14, 2005; ACCEPTED JANUARY 18, 2005

The method of overlapping spheres (OS) was applied to the estimation of stability constants of mono- (log β_{110}) and bis-complexes (log β_{120}) of α-amino acids and their *N*-alkyl and *N,N*-dialkyl derivatives with copper(II). The central sphere, with a 0.3 or 0.4 nm radius, was placed at the central (Cu), equatorial (N) or apical (X) position of the coordination polyhedron. The overlapping volume of the central sphere and the van der Waals spheres of neighbouring atoms was calculated and correlated with the measured stability constants. The training set (N = 11) consisted of four naturally occurring amino acids and seven *N*-alkylated and *N,N*-dialkylated glycines. It gave, upon linear regression of stability constants on the overlapping volume, correlation coefficients (r) of 0.944 and 0.895 for log β_{110} and log β_{120}, respectively. The best regressions (r = 0.977–0.998) were obtained by taking into account only the complexes of *N*-alkylated glycine (N = 5) and placing the central sphere at the position of equatorial nitrogen atom(s). Using the regression functions derived from the training set, it was possible to estimate the measured stability constants with an error in the range 0.1–0.5 log β units.

Keywords
N-alkylated amino acids
molecular volumes

INTRODUCTION

The overlapping spheres (OS) method is based on the calculation of the overlapping volume of van der Waals spheres of constituent atoms, or any spheres defined in a systematic way. This constitutes the OS method, a sort of computational procedure based on the modelling of molecular volumes,[1–3] or to be more specific, the OS method stems from Hopfinger and Scheraga's hydration shell model for calculating the Gibbs energy of solvation,[4–8] or more generally from the methods based on the continuous distribution of the solvent.[9] The method has been applied in drug design,[10–12] as well as in conformational[13–17] and topological analyses.[18–20]

In my first application of the overlapping spheres method to coordination compounds,[21] I used the method in a classical stereochemical problem – enantioselectivity effects in copper(II) chelates with amino acids.[22–27] Using the OS method it was possible to calculate the sterical energy difference between the conformers of copper(II) chelates with *N,N*-dialkylated amino acids, yielding a difference less than 5 kJ mol^{-1} compared to the values obtained by molecular mechanics.[21] The aim of this paper is to make a further step, *i.e.*, it is intended for the development of a general procedure for estimation of stability constants of coordination compounds. The proposed procedure should calculate the Gibbs energy difference between constitutionally different molecules, not

* Dedicated to Dr. Edward C. Kirby on the ocassion of his 70th birthday.

different conformers or stereoisomers, as the methods based on the molecular-mechanics approach do. In this respect, the paper should be regarded as a continuation of our work on estimation of stability constants of copper(II) chelates with amino acids by using molecular descriptors (notably topological indices).[28,29]

METHODS

The overlapping spheres (OS) approach is based on the evaluation of the function:[30]

$$V^* = \Sigma\ V_j(S_v \cap s_j) \qquad (1)$$

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 neighbouring atoms (calculation details along with the set of van der Waals radii are given elsewhere).[14] The central sphere is situated at the central atom (Cu) or at atoms (N, O, X) in the first coordination sphere (Figure 1). Letter X marks two apically situated »dummy« atoms (Cu-X = 0.250 nm). In all calculations, the overlapping volume of the central sphere and the atom at which it was situated was not taken into account. Biscompexes were treated as *trans*-isomers.

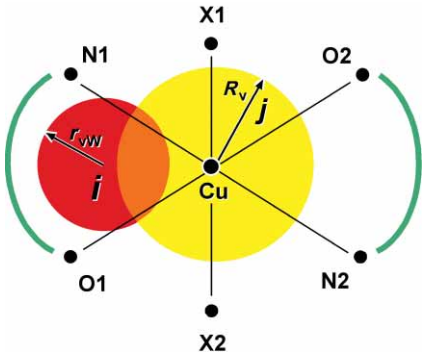

Figure 1. General scheme of the model of overlapping spheres (*cf.* Eq. 1). Central sphere is situated at the copper atom.

For the two atoms in *trans*-position (*e.g.,* N1 and N2, Figure 1) the common overlapping spheres volume was calculated simply as a sum of the elementary volumes:

$$Os_1(N1,N2) = V^*(N1) + V^*(N2) \qquad (2)$$

The equation, however, yielded unsatisfactory results if the elementary volumes differed too much. Therefore, I was forced to choose a function that should be less dependent on that difference and I applied it to the apical substituents (X1, X2), the overlapping volumes of which differ considerably in:

$$Os_2(X1,X2) = [V^{*2}(X1) + V^{*2}(X2)]\ [V^*(X1) + V^*(X2)]^{-1} \qquad (3)$$

Function (3) can be also written in the form:

$$Os_2(X1,X2) = 0.5\ Os_1 + [\{0.5\ Os_1 - V^*(X1)\}^2 + \{0.5\ Os_1 - V^*(X2)\}^2]\ Os_1^{-1} \qquad (4)$$

It is evident that $V^*(X1) < Os_2(X1,X2) < Os_1(X1,X2)$ generally holds, assuming $V^*(X1) > V^*(X2)$. In special cases, $Os_2(X1,X2) = 1/2Os_1(X1,X2) = V^*(X1) = V^*(X2)$, for $V^*(X1) = V^*(X2)$, and $Os_2(X1,X2) = Os_1(X1,X2) = V^*(X1)$, for $V^*(X2) = 0$.

Calculation of the overlapping volume of the central sphere and the neighbouring atoms (Eq. 1) was performed by a special FORTRAN program. All molecular mechanics calculations, needed to find the conformers of copper(II) chelates with amino acids, were done with the program developed by Kj. Rasmussen and co-workers,[31–33] using the force field denoted as FF3a,[34,35] capable of simulating distortion of the copper coordination polyhedron.

The stability constants (log $ß_{110}$ and log $ß_{120}$), taken from the literature, were measured at 25 °C and I = 0.1 mol L^{-1} (if available).

RESULTS AND DISCUSSION

Mono-complexes

For the training set, the 11 log $ß_{110}$ and log $ß_{120}$ values for the complexes of four amino acids (Gly,[36] Ala,[37] Val,[37] Leu[38]), five *N*-alkylated amino acids (MeGly, EtGly, PrGly, BuGly, iPrGly)[36] and two *N,N*-dialkylated amino acids (Me_2Gly, Et_2Gly)[36] were taken from the literature. If the complex had few (1–5) conformations (chelates of Gly, Ala, MeGly, Me_2Gly, and iPrGly), all conformations were taken into account. For the rest of the molecules, only representative conformations were calculated: four conformations for Cu(Val), Cu(PrGly), and Cu(BuGly), three conformations for Cu(Et_2Gly), and two conformations for Cu(Leu) and Cu(EtGly). The overlapping volume appears to be more dependent on the conformation of the chelate ring than on the conformation of the side chain(s). Moreover, the apical position (X1, X2) is more dependent on the molecular conformation than other positions.

Results of linear regression of the stability constant log $ß_{110}$ on overlapping volumes for all 11 complexes (training set) are presented in Table I, and partially in Figure 2. The radius of the central sphere, R_v, was fixed at 0.3 or 0.4 nm. As the stability constant is dependent on the energy (*i.e.,* overlapping volume) of all conformers (Boltzmann distribution!), which cannot be calculated at this level of approximation, two extreme cases are separately discussed. If a molecule has a large number of conformations, which are very close in energy, the energy of the system can be satisfactory approximated by

TABLE I. Linear regressions of the stability constant log β_{110} on the overlapping volumes of 11 chelates of amino acids with copper(II)

No.	Sphere position	R_v/nm	Independent variable	Slope (S.E.)[(a)]	Intercept (S.E.)[(a)]	r
1	Cu	0.3	V^*_{min}	–0.0554(93)	11.00(58)	0.893
2	Cu	0.4	V^*_{min}	–0.0222(33)	10.09(37)	0.915
3	Cu	0.3	$\langle V^* \rangle$	–0.0582(83)	11.317(54)	0.919
4	Cu	0.4	$\langle V^* \rangle$	–0.0225(32)	10.27(39)	0.918
5	N	0.3	V^*_{min}	–0.0230(34)	9.946(359)	0.913
6	N	0.4	V^*_{min}	–0.0156(37)	9.755(526)	0.814
7	N	0.3	$\langle V^* \rangle$	–0.0231(34)	10.00(36)	0.915
8	N	0.4	$\langle V^* \rangle$	–0.0143(37)	9.590(54)	0.784
9	X1, X2	0.3	Os_2^{min}	–0.0914(19)	10.31(66)	0.812
10	X1, X2	0.4	Os_2^{min}	–0.0477(55)	11.26(43)	0.944
11	X1, X2	0.3	$\langle Os_2 \rangle$	–0.0227(21)	8.503(857)	0.341
12	X1, X2	0.4	$\langle Os_2 \rangle$	–0.0277(107)	10.02(95)	0.652

[(a)] Values in parentheses refer to last decimal places.

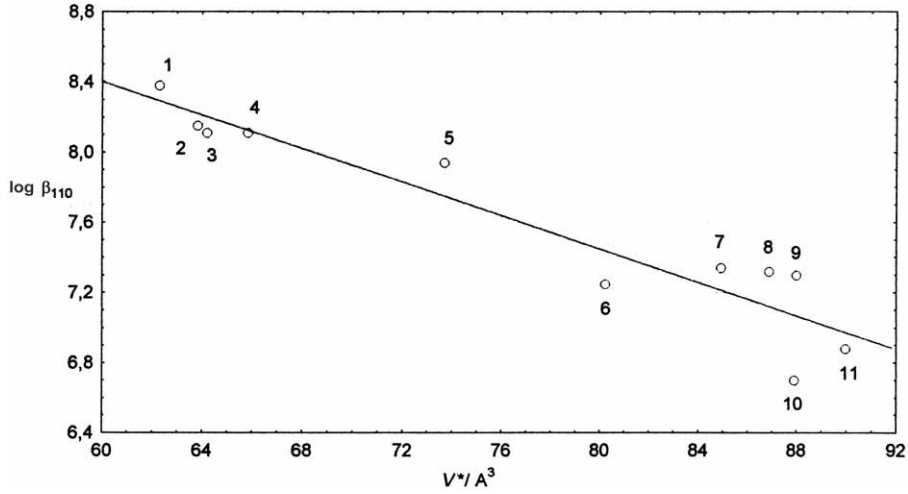

Figure 2. Regression line of log β_{110} *vs.* Os_2^{min}(X1,X2), r = 0.944 (No 10, Table I). Ligand notation: Gly (1), Ala (2), Val (3), Leu (4), MeGly (5), PrGly (6), EtGly (7), BuGly (8), Me_2Gly (9), iPrGly (10), Et_2Gly (11).

the mean energy of all conformations. In another extreme case, when the energy of one conformation is substantially lower than the energy of all other conformations, the energy of the system approaches the energy of the lowest-energy conformation. Therefore, the overlapping volume of the molecule was calculated in two ways. It was chosen as the value for the conformation with the smallest OS volume or, alternatively, as the mean OS volume of all the molecular conformations calculated. If all conformations were not known, the mean value was calculated from the equal number of conformations differing in chirality and/or conformation of the chelate ring.

The results obtained at the Cu and N positions speak slightly in favour of the minimal-value approach ($\langle r \rangle$ = 0.884 for both sets, but the range of r value, 0.814–0.915 *vs*. 0.784–0.919, is better for the minimal-value set). Moreover, the average-value method gave rather unsatisfactory results for apical (X1, X2) atoms. This finding could be possibly attributed to the fact that the apical position is more dependent on molecular conformation than other positions. Position of the central sphere on oxygen atom (O) yielded entirely unacceptable results (r < 0.5 for all models), and it will not be discussed further.

Linear regressions calculated on the training set were checked against the experimental data for copper(II) complexes. One representative of each of the three groups of compounds was selected (Table II): norvaline (amino acids), *N-tert*-butylglycine (*N*-alkylated amino acids), and *N*-methyl-*N-tert*-butylglycine (*N,N*-dialkylated amino acids). The results for complexes of norvaline and *N-tert*-butylglycine fit well the experimental data, but the error approaches 0.5 log β units for the chelate with *N*-methyl-*N-tert*-butylglycine. Slightly better results ($\Delta \log \beta_{110}$ = 0.466 *cf*. 0.628) were obtained for the latter complex when the calculated extreme values were not taken into account, but the approach did not succeed for the *N-tert*-butylglycine complex. The best results, however, were obtained from the regressions only on complexes

TABLE II. Comparison of the measured and calculated values of log β_{110} for two copper(II) chelates with *N*-alkylated amino acids. Values were calculated as an average over six regressions (No. 1, 2, 5, 6, 9 and 10, Table I).

Ligand	Calculated (mean value)	Standard error of the calculated value	Measured value
2-aminopentanoic acid (norvaline)	8.02	0.211	8.07–8.17[c]
	8.15[a]	0.04[a]	
N-*tert*-butylglycine	6.365	0.705	6.059–6.303[d]
	6.809[b]	0.058[b]	
	6.122[e] (6.060)[f]	0.085[e]	
N-methyl-*N*-*tert*-butylglycine	6.102	0.252	6.730[d]
	6.264[b]	0.028[b]	

[a] Results of regressions 5 and 6 were not taken into account.
[b] Results of regressions 9 and 10 were not taken into account.
[c] Lower value: I = 0.2 mol L^{-1} (KCl), Ref. 39; higher value I = 0.05 mol L^{-1} (KCl), Ref. 40; T = 298.15 K.
[d] Taken from Ref. 28: I = 0.1 mol L^{-1} (KNO_3), T = 298.15 K.
[e] Calculated from the regressions made only on the complexes of *N*-alkylated amino acids (N = 5); the centre of the sphere is situated at the N atom (Regr. 1: R_v = 0.3 nm, Slope = –0.0474(17), Intercept = 12.409(187), r = 0.998; Regr. 2: R_v = 0.4 nm, Slope = –0.0215(27), Intercept = 10.364 (390), r = 0.977).
[f] Weighted value: $\log \beta_{110}^{calc} = [r_1^2 (\log \beta_{110}^{calc})_1 + r_2^2 (\log \beta_{110}^{calc})_2]/2 \; (r_1^2 + r_2^2)$.

with *N*-alkylated amino acids. In that case, very high values of regression coefficients were reached ($r > 0.97$), and the estimated stability constant ($\log \beta_{110} = 6.122(85)$ had virtually the same value as the mean of three measurements of the *N*-*tert*-butylglycine complex ($\log \beta_{110} = 6.152(132)$.[28] Substantially better results obtained by using regression only on complexes of *N*-alkylated amino acids suggest that the OS method deals satisfactory with the steric factors affecting the stability of coordination compounds, but fails to cope with the electronic effects. It should be noted that three kinds of Cu-N bonds are present in the basic training set (Cu-NH_2R, Cu-NHR_2, and Cu-NR_3) and thus the electronic effect should be considerable.

Bis-complexes

For bis-complexes, the same set[36–38] of stability constants was used as for mono-complexes. The only exception was Bretton's value of stability constant for leucine, which was judged to be unrealistically high ($\log ß_{120} = 15.84$),[38] so it was replaced with a more realistic value ($\log ß_{120} = 14.34$),[39] albeit measured at I = 0.01 mol L^{-1}. All conformations were taken into account for the copper(II) complexes with glycine, alanine, *N*-methyl-, and *N,N*-dimethylglycine. Five conformations were calculated for valine, *N*-prolylglycine, *N*-butylglycine, and *N*-isopropylglycine. Leucine and *N,N*-diethylglycine were represented by three and the complex with *N*-ethylglycine by six conformations. As the purpose of conformational analysis was to find the conformation with the lowest value of the OS volume, conformations of mono--complexes with the lowest OS volumes were combined.

The six linear regressions of $\log ß_{120}$ on minimal values of the overlapping spheres volumes (Table III) show a less satisfactory agreement with the experimental data ($\langle r \rangle = 0.870$) than the regressions for mono-complexes. However, the range of values (r = 0.835–0.895) indicates better homogeneity of the results. Residuals of the best regression (No. 3, Table III, Figure 2) are in the range 0.06–0.82 (mean = 0.31). This is about twice worse than the best results (No. 10, Table I, Figure 3) for mono-complexes ($|\Delta \log \beta_{120}|$ = 0.02–0.37, mean = 0.15). Moreover, the calculated values of $\log ß_{120}$ (Table IV) on the same set of ligands (with the exception of bis-(*N*-methyl-*N*-*tert*-butylglycine)copper(II), which is not referred to in literature) show a difference from experimental data of 0.28 and 0.485 log β units for norvaline and *N*-*tert*-butylgycine, respectively (compared to 0.05

TABLE III. Linear regression of the stability constant log β_{120} on the overlapping volumes of 11 chelates of amino acids with copper(II)

No.	Sphere position	R_v/nm	Independent variable	Slope (S.E.)[a]	Intercept (S.E.)[a]	r
1	Cu	0.3	V^*_{min}	–0.0426(80)	19.13(99)	0.871
2	Cu	0.4	V^*_{min}	–0.0164(29)	17.59(67)	0.881
3	N	0.3	Os_1^{min}	–0.0177(29)	17.81(66)	0.895
4	N	0.4	Os_1^{min}	–0.0115(22)	17.87(79)	0.863
5	X1, X2	0.3	Os_2^{min}	–0.0534(17)	16.89(67)	0.835
6	X1, X2	0.4	Os_2^{min}	–0.0276(51)	17.99(77)	0.874

[a]Values in parentheses refer to last decimal places.

TABLE IV. Comparison of the measured and calculated values of log β_{120} for two copper(II) chelates with *N*-alkylated amino acids. Values were calculated from all the six regressions in Table III.

Ligand	Calculated (mean value)	Standard error of the calculated value	Measured value
2-aminopentanoic acid (norvaline)	14.536	0.244	14.82–15.04[a]
N-tert-butylglycine	12.662	0.316	12.177[d]
	11.591[b]	0.136[b]	
	12.394[c]	0.281[c]	

[a] Lower value: I = 0.2 mol L^{-1} (KCl), Ref. 39; higher value I = 0.05 mol L^{-1} (KCl), Ref. 40; T = 298.15 K.
[b] Calculated from the regressions made only on the complexes on *N*-alkylated amino acids (N = 5); the centre of the sphere is situated at the N atom (Regr. 1: R_v = 0.3 nm, Slope = –0.0388(19), Intercept = 22.401(443), r = 0.996; Regr. 2: R_v = 0.4 nm, Slope = –0.0161(19), Intercept = 19.219(682), r = 0.978).
[c] Result of all the 8 regressions.
[d] Ref. 28.

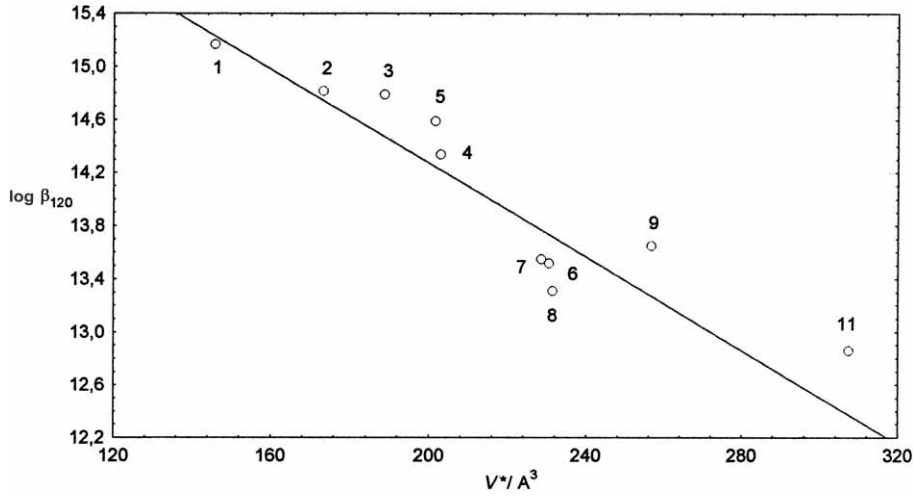

Figure 3. Regression line of log β_{120} *vs.* Os_1(N1,N2), r = 0.895 (No 3, Table III). Ligands are denoted according to the scheme in Figure 2.

and 0.062 log β units difference for mono-complexes, Table II). Linear regressions on only *N*-alkylated amino acids did not improve the results, in spite of better correlation coefficients, which is an indication that in the case of *N-tert*-butylglycine some additional factors influence chelate stability. It is well known that in solutions of *N*-alkylated amino acids complex equilibria between a number of isomers take place (*cis*, *trans*, *aqua*, cage and polymeric complexes) and the variation rises with the steric hindrance of the ligand.[24]

CONCLUSION

The results presented in this paper point to the following conclusions:

(i) The method based on the model of overlapping spheres is capable of reproducing the stability constants of copper(II) chelates with amino acids in the range of 0.1 to 0.5 log β units. Sometimes, the margins of experimental error can be reached;

(ii) The method does not deal with the electronic effects affecting the stability. Precaution is therefore needed when the method is applied to a heterogeneous set of compounds;

(iii) For the application of the method, the knowledge of chelate conformations is required, as well as the structure (*i.e.,* isomerism) of the complex existing in solution.

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SAŽETAK

Procjena konstanti stabilnosti bakrovih(II) kelata s aminokiselinama metodom preklapanja kugli

Nenad Raos

Metoda preklapanja kugli (*overlapping spheres*, OS) primijenjena je za procjenu konstanti stabilnosti mono-kompleksa (log β_{110}) i bis-kompleksa (log β_{120}) α-aminokiselina i njihovih *N*-alikiliranih i *N,N*-dialikiliranih derivata s bakrom(II). Središnja kugla, radijusa 0,3 ili 0,4 nm, postavljena je u središnji (Cu), ekvatorijalni (N) ili apikalni (X) položaj koordinacijskoga poliedra. Izračunan je volumen preklapanja središnje kugle i van der Waalsovih kugli okolnih atoma te je zatim koreliran s izmjerenim konstantama stabilnosti. Temeljni skup (N = 11) sastojao se od četiri prirodne aminokiseline i sedam *N*-alikiliranih i *N,N*-dialikiliranih glicina. Linearnom regresijom konstanti stabilnosti prema volumenu preklapanja postignut je iz temeljnog skupa koeficijent korelacije (r) u iznosu od 0,944 za log β_{110} i 0,895 za log β_{120}. Najbolje regresije (r = 0,977–0,998) dobivene su iz podataka samo za *N*-alkilirane glicine (N = 5), pri čemu se središnja kugla nalazila na ekvatorijalnome (dušikovome) atomu ili atomima. Iz regresijskih funkcija razvijenih na temeljnome skupu izračunane su konstante stabilnosti koje su se od izmjerenih vrijednosti razlikovale za 0,1 do 0,5 log β jedinice.