Estimation of Conformational Energy
of Coordination Compounds by Using the Model
# of Overlapping Spheres

Nenad Raos

Institute for Medical Research and Occupational Health, Zagreb, Croatia

The newly proposed method for the estimation of conformational energy is based on the assumption that the sterical strain is proportional to the occupancy of the volume (defined by the sphere of radius R_{vi}) by the van der Waals spheres of the neighbouring atoms. The method was checked on planar copper(II) bis- and aquabis-complexes with *N*-alkylated amino acids, yielding the correlation coefficient between the conformational energy and the sterical parameters up to $r = 0.95$. The proposed method has been proved not to be very dependent on the exact geometry of the molecule or the calculation procedure, but it does not seem to be very reliable for small energy differences between the conformations (< 3–5 kJ mol^{-1}). Its future application should, therefore, be viewed as a tool for an easy elimination of high-energy conformations.

INTRODUCTION

There is little doubt that the problem of finding the global minimum (*i.e.* the most stable conformer) is the most challenging problem of conformational analysis. There have been many attempts to solve that problem,[1] but a general – or only quite efficient – method has not been given yet. There are three general approaches to solving the problem of the global minimum. The first approach seeks to find conformers that dominate in a particular class of compounds by analyzing the experimental data (*e.g.* by inspecting the crystallographic data bank). The second set of methods is based on construction of the final conformation from molecular fragments

(conformational units),[2, 3] assuming that the energy of the final conformation approximately equals the summed up energy of its fragments (subconformations). The most sophisticated methods are based on »global minimization«, *i.e.* on the movement of the molecule in search of the global minimum[4–7] on the potential energy surface. Various combinations[8, 9] and variations (*e.g.* genetic algorithm[10]) of the methods have also been used in the practice.

None of the above mentioned approaches is perfect. The assumption that the most stable conformer appears in the crystal state enabled construction of the Ramachandran plot,[11] but if a molecule is small and intermolecular interactions in the crystal lattice are strong, such a simple assumption can be totally misleading. For instance, none of the six conformationally analyzed pentacoordinated (aqua) *N*-alkylated copper(II) aminoacidates[12–17] appeared in the most stable conformation in the crystal state.

The build-up of molecular conformations from conformational units is based on the assumption that the final energy can be calculated by simple addition of the energy of the constituting fragments, and that the interaction energy of fragments can be easily estimated, *e.g.* from the energy of molecular conformation before minimization of the conformational energy. However, the last assumption is wrong, for the energy of initial conformation strongly depends on very small differences in molecular geometry and does not essentially correlate with the energy of minimized conformation.

The aim of this paper is to propose a new method for the estimation of conformational energy (or, more precisely, of the interaction energy between conformational units) based on the concept of the overlapping sterical volume. This model was initially developed to calculate the solvation (hydration) energy of the proteins,[18, 19] but was also applied to the calculation of solvation energy of coordination compounds.[20] The concept of overlapping van der Waals spheres led Hopfinger to propose a concept of a common overlap steric volume and use it as a measure of molecular similarity in QSAR analysis.[21]

The assumption that the interaction energy between molecular fragments is proportional to the »occupancy of the space« in the molecule, as the basic idea of the new method, is in accordance with the chemical intuition, and therefore the method can be regarded as a heuristic approach to the problem of the global minimum. To test it, I have chosen the class of copper(II) chelates with *N*-alkylated amino acids[22] because they have been well investigated, both conformationally and crystallographically. These are also compounds with a great number of possible conformers; for instance, the number of conformations of *trans*-isomer of aquabis(*N*,*N*-diethylleucinato)-copper(II) can be predicted to be 26 406.

METHODS

The overlapping volume is defined (Figure 1) as an intersecting volume of the sphere i (V_i) with the radius R_{vi} and the van der Waals sphere (v_j) of the atom j, having the radius r_j, *i.e.* $V_i \cap v_j$.
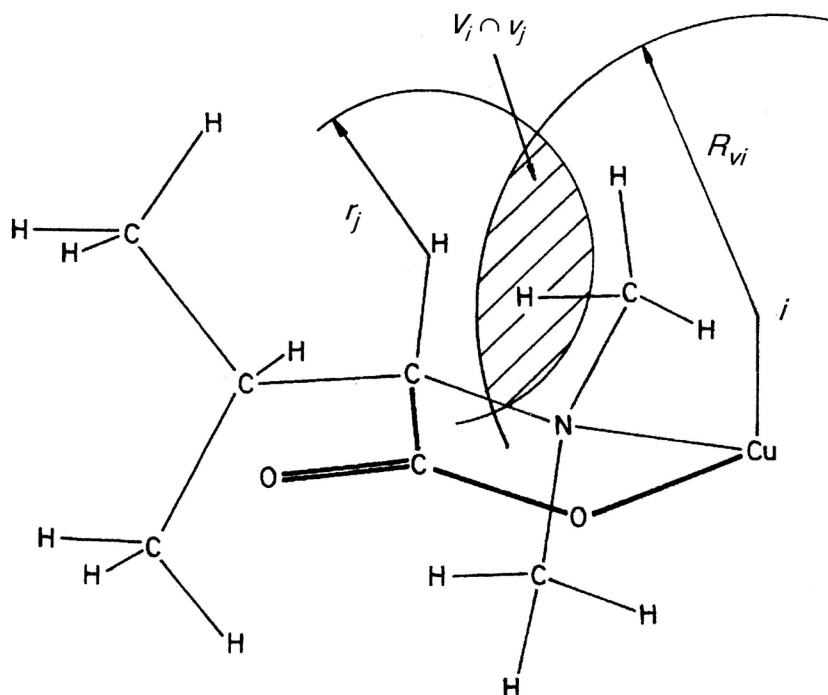

Figure 1. Scheme of the model. The interacting sphere is situated at the apical position on the H-side of the chelate ring of the *N,N*-dimethylvaline complex in the equatorial conformation.

There are three possible cases:[19]

1.) $V_i \cap v_j = 0$ when $R_{vi} + r_j \leq r_{ij}$,

where r_{ij} is the distance between the centers i and j.

2.) $V_i \cap v_j = \frac{4}{3}\pi r_j^3$ when $r_j + r_{ij} \leq R_{vi}$

3.) When $R_{vi} + r_j > r_{ij}$

$$V_i \cap v_j = \frac{1}{3}\pi\left[2R_{vi}{}^3 + 2r_j{}^3 + r_{ij}{}^3\right] - \pi\left[R_{vi}{}^2x^* + (r_{ij} - x^*)(r_j{}^2 + r_{ij}x^*)\right] \qquad (1)$$

where

$$x^* = (R_{vi}{}^2 - r_j{}^2 + r_{ij}{}^2)/2r_{ij} \qquad (2)$$

The total overlapping volume of atom i is:

$$V_i{}^* = \sum_j (V_i \cap v_j) \qquad (3)$$

Also, for a quite practical reason, the occupational density of the sphere i was defined as:

$$d_i = \frac{V_i{}^*}{\frac{4}{3}\pi R_{ij}{}^3} \qquad (4)$$

If two sides of the chelate ring were denoted with a and b, and if the second chelate ring was marked with an apostrophe, the sterical function for *trans*-LL isomer could be defined as:

$$S_{LL} = \left[(d_a + d_a')^2 + (d_b + d_b')^2\right]^{\frac{1}{2}} \qquad (5)$$

and for *trans*-DL isomer an analogous function is expressed by:

$$S_{DL} = \left[(d_a + d_b')^2 + (d_b + d_a')^2\right]^{\frac{1}{2}} \qquad (6)$$

If a water molecule is apically ligated, its »density« (w) is also added. For instance, if the molecule is LL isomer, and the water molecule is bonded from the a-side of the ring:

$$S_{LL} = \left[(d_a + d_a' + w)^2 + (d_b + d_b')^2\right]^{\frac{1}{2}} \qquad (7)$$

It was assumed that for the water molecule r_j equals 1.35 Å (van der Waals radius of the oxygen atom); therefore $w = 0.1575$ for $R_{vi} = 2.5$ Å and $w = 0.729$ for $R_{vi} = 1.5$ Å.

The centre of sphere i was usually placed in an apical position (*i.e.* at the C_2 or S_2 (pseudo)axis of the molecule) at the distance $l_0 = 1.0$ Å from the copper atom. It was found necessary to calculate the overlapping volume only for atoms from the side of the chelate ring where the centre of the sphere was situated. The overlapping volume with the central atom was disregarded in all calculations.

RESULTS AND DISCUSSION

Example 1. Complexes of N,N-Dimethylalanine

The first example shows the molecule of bis(L-N,N-dimethylalaninato)copper(II) and its aqua complex. Since the chelate ring appears only in two conformations (axial and equatorial), the bis-complex has three conformers (a-a, a-e and e-e), and the aqua-complex molecule has six isomeric forms due to two possible positions of water molecule (denoted as the H-side and R-side positions).

Results of the d function (Figure 2) and of the S function calculation (Table I) showed that the general result was not strongly dependent on the in-
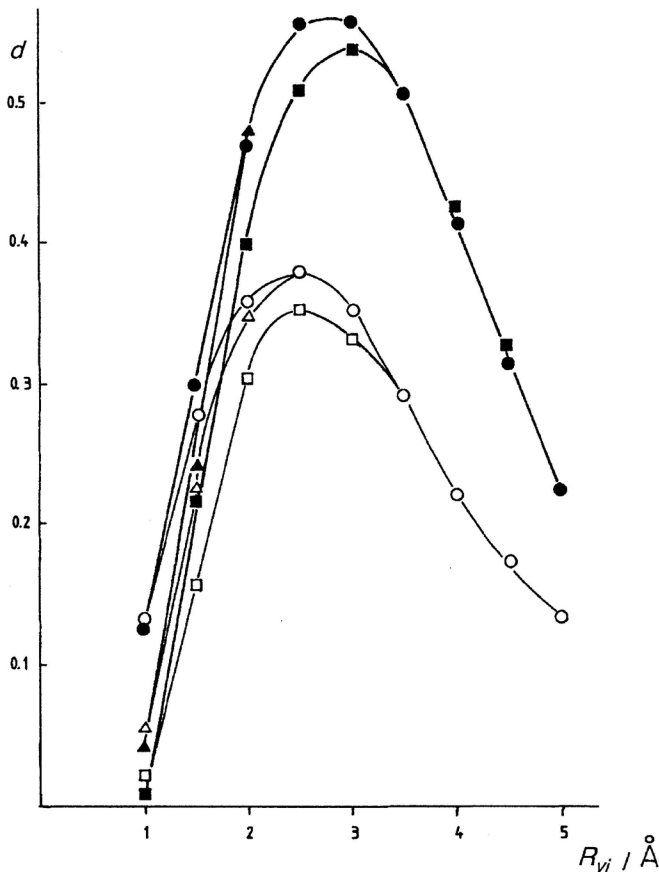

Figure 2. Influence of parameters l_0 and R_{vi} on occupational density d of the sphere placed on the R-side of the N,N-dimethylalaninatocopper(II) molecule. Circles, triangles and squares denote l_0 values of 0.5, 1.0 and 1.5 Å, respectively. Full and empty figures denote the axial and equatorial conformation of the chelate ring, respectively.

TABLE I

Conformational energy (V) and sterical function (S) for two copper(II) chelates with N,N-dimethylalanine[a]

Conformer	ML$_2$			ML$_2$–OH$_2$					
				H-side			R-side		
	V	S_1	S_2	V	S_1^w	S_2^w	V	S_1^w	S_2^w
a-a	0.00	1.3638	0.6667	0.00	1.4581	1.2855	8.20	1.4968	1.2939
a-e	2.41	1.2855	0.6527	1.13	1.3967	1.2706	6.43	1.4057	1.2831
e-e	2.67	1.2375	0.6388	1.42	1.3646	1.2557	2.78	1.3409	1.2724

[a] Function S_1 corresponds to $R_{vi} = 2.5$ Å, and S_2 to $R_{vi} = 1.5$ Å. In both cases the center of the sphere was placed apically at $l_0 = 1.0$ Å from the central atom. Conformational energy (V) is expressed in kJ mol^{-1} and taken from Ref. 17.

eractiong sphere radius, R_{vi}, or on the distance of the sphere centre from the copper(II) atom. The example in Figure 2 shows that the difference in d between two conformers is not very dependent on R_{vi} and l_0. This also holds for the initial molecular geometry from which d has been calculated. The equatorial conformation of the chelate ring has the following parameters: $d_a = 0.3735 - 0.3890$ (mean = 0.3842, S.D. = 0.0058) and $d_b = 0.4621 - 0.4856$ (mean = 0.4711, S.D. = 0.0089) at $l_0 = 1.0$ Å and $R_{vi} = 2.5$ Å, taking into account 10 structures obtained by using different force fields, conformations (e-e and e-a) and molecular complexes (ML, ML$_2$ and ML$_2$-OH$_2$).[17]

The method correctly predicted that R-side aqua-isomers should be more strained than their H-side analogs. The preference in energy for R-side conformers was also correctly predicted, but the method gave erroneous results for the other two complexes. This result cannot even be attributed to the difference in energy between equatorial and axial conformation of the chelate ring. Namely, molecular mechanics calculations with the force field FF3a[23] yielded 12.595 kJ mol^{-1} for the axial ML complex, and 12.031 kJ mol^{-1} for the equatorial conformer.

However, a comparison of conformational energies shows that erroneous results appeared only for small differences in energy, while for higher differences (> 3 kJ mol^{-1}) the S function gave results consistent with molecular mechanics calculations and also with stereochemical intuition.

Example 2. Bis(N,N-dimethylvalinato)copper(II)

Copper complexes with N,N-dimethylvaline are the conformationally best studied complexes in the class of N-alkylated aminoacidates. Due to six conformations of the chelate ring (equatorial ones, denoted 1-3 and axial conformations, denoted 4-6), the complex has 21 conformations. Moreover,

there is a pronounced enantioselectivity effect (difference in thermodynamic stability between the MLL and MDL complexes) measured in the system of copper chelates with N,N-dimethylvalines.[24] The effect was later attributed to the difference in energy between the conformers of MLL and MDL isomers.[25-29]

Table II shows a very high correlation of both isomers in conformational energy on S function. The plot of the regression line for the MDL isomer (Figure 3) shows that it is possible to estimate the interaction energy of the chelate rings with an error margin less than 4 kJ mol^{-1} (20% of the maximum value). The proposed method proved also valuable in predicting the enantioselectivity effect (Table III). From the sterical parameters and approximate energy of bis-complex (calculated by assuming that it equals the sum of the conformational energy of two »monocomplexes« forming its chelate rings), it is obvious that the MLL complex should be less stable than the MDL isomer, and that the decrease in stability should be mainly attributed to the difference in energy between two epimeric 6-6 conformers. This simple conclusion can be obtained by evaluating the energy of only six monocomplex conformers and is quite in accordance with the more rigorous mo-

TABLE II

Linear regression of conformational energy on sterical function S[a]

Compound	Isomer(s)	Regression function	Regression variable		Regression parameters[b]	
				N	r	p
$(Me_2Val)_2Cu$	LL	$V - V_{ap}$	S_{LL}	21	0.6558	0.0012
$(Me_2Val)_2Cu$	DL	$V - V_{ap}$	S_{DL}	21	0.9493	<0.0001
$(Me_2Val)_2Cu$	LL, DL	$V - V_{ap}$	S_{LL}, S_{DL}	42	0.7777	<0.0001
$(Me_2Val)_2Cu$	LL, DL	$V_{LL} - V_{DL}$	$S_{LL} - S_{DL}$	21	0.6659	0.0010
$(Me_2Val)_2Cu\text{-}OH_2$	LL	$V_H - V_{ap}$	S_H^w	21	−0.6479	0.0015
$(Me_2Val)_2Cu\text{-}OH_2$	LL	$V_H - V_{ap}$	S_H^w	15	−0.8692	<0.0001
$(Me_2Val)_2Cu\text{-}OH_2$	LL	$V_H - V_{ap}$	S_H^w	6	0.9338	0.0064
$(Me_2Val)_2Cu\text{-}OH_2$	LL	$V_R - V_{ap}$	S_R^w	21	0.8119	<0.0001
$(Me_2Val)_2Cu\text{-}OH_2$	LL	$V_R - V_H$	$S_R^w - S_H^w$	21	0.9479	<0.0001
$(Me_2Val)_2Cu\text{-}OH_2$	DL	$V_R - V_H$	$S_R^w - S_H^w$	15	0.8656	<0.0001

[a] Energy values (V) are expressed in kJ mol^{-1} and data for bis(N,N-dimethylvalinato)copper(II) and aquabis(N,N-dimethylvalinato)copper(II) are taken from Ref. 23 and 14, respectively. Labels R and H denote C^α-R and C^α-H side isomers (see Example 1). V is the energy obtained by MM calculations, and V_{ap} is the approximate energy calculated by the method of overlapping spheres (in the same way as in Table III). R_{vi} = 2.5 Å, l_0 = 1.0 Å.

[b] N, number of data points; r, regression coefficient; p, probability of correlation by pure chance.
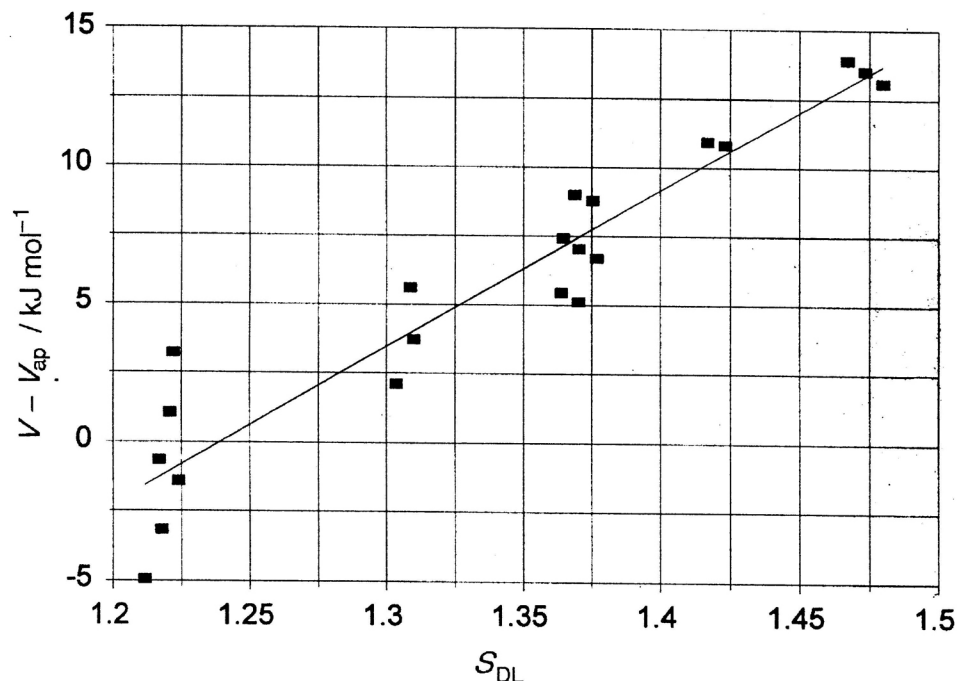
Figure 3. Regression line of energy difference between the calculated[23] and estimated (see Table II) conformational energy of bis(D,L-*N*,*N*-dimethylvalinato)copper(II). Slope = 56.993 (S.E. = 4.330), inercept = −70.630 (S.E. = 5.804), r = 0.9493.

lecular mechanics calculations. Namely, conformer 6-6 contributes to the conformer population by more than 85% in both isomers,[25-29] making it clear that this conformer is most responsible for the observed enantioselectivity effect. Table III shows two energy values (obtained with force fields FF1 and FF2) for the difference between MLL and MDL conformers. Because of the very high value of angle-bending parameters for copper, the force field FF1 yielded nearly square-planar structures and a higher enantioselectivity effect (11.75 kJ mol^{-1})[25] than measured (2.9–4.0 kJ mol^{-1}).[24] By using the force field FF2 (with lower values of angle-bending parameters), results within the limits of experimental error were obtained (3.73 kJ mol^{-1}).[26, 29] It is noteworthy that, despite the moderate correlation of the $V_{LL} - V_{DL}$ on $S_{LL} - S_{DL}$ (r = 0.6659), the group of three epimeric conformer pairs (6-6, 5-6 and 5-5) with ΔS values 0.014 higher than the ΔS value for the conformers from the closest group (4-4, 4-5 and 4-6) have a distinctively higher energy difference between MLL and MDL conformers than any other groups (Table III). The less successful prediction of the energy difference between MLL and MDL conformers obtained with FF2 is a natural consequence of smaller energy values.

TABLE III

Estimation of the conformational energy of the
bis(N,N-dimethylvalinato)copper(II) isomers[a]

Conformer[b]	V estimated[c]	$S_{LL} - S_{DL}$	$V_{LL} - V_{DL}$ calculated	
			FF1	FF2
6-6	0.00	0.0571	10.42	3.48
1-6	5.96	−0.0151	0.31	0.10
3-4	8.58	0.0040	0.32	2.36
3-6	8.85	−0.0150	0.13	1.29
4-6	10.73	0.0432	0.37	−0.70
5-6	15.43	0.0572	8.72	2.22
2-6	17.47	−0.0160	0.42	1.26
3-3	17.70	−0.0159	−0.67	−5.99
1-3	18.81	0.0040	−0.42	−2.92
3-5	19.58	0.0040	0.32	
1-1	19.92	0.0040	−0.26	
1-4	20.69	−0.0120	0.08	
4-4	21.46	0.0327	−1.33	
4-5	25.16	0.0433	−0.55	
1-5	25.39	−0.0150	0.42	
2-3	26.32	0.0046	−0.54	
1-2	27.43	0.0064	−0.33	
2-4	28.20	0.0042	0.13	
5-5	30.86	0.0572	7.54	1.06
2-5	32.90	0.0122	0.62	
2-2	34.94	−0.0151	−0.43	

[a] Energy values are taken from Ref. 23 (FF1) and Ref. 28 (FF2). Energy (V) is expressed in kJ mol^{-1}. $R_{vi} = 2.5$ Å, $l_0 = 1.0$ Å.

[b] As denoted in Ref. 25. Conformers 1 to 3 and 4 to 6 have equatorial and axial positions of the side (isopropyl) group in the chelate ring. Conformations of the side chain are g^- (1 and 6), g^+ (3 and 4), t (2 and 5).

[c] Calculated as the sum of energy of two constituting chelate rings: $V(ML_a L_b) = V(ML_a) + V(ML_b)$.[23]

Example 3. Aquabis(N,N-dimethylvalinato)copper(II)

The complex appears in two forms, as a MLL and a MDL isomer (only the MLL isomer was observed in the crystal state),[14] with 42 possible conformers of the MLL and 30 conformers of the MDL isomer, due to two possible positions of ligand water. The linear regression of the »excess« of conformational energy above its approximate value ($V - V_{ap}$) on S^w (Table II) yielded a high positive correlation coefficient only for R-sided conformers of the MLL

isomer ($r = 0.8119$). The energy of H-sided conformers, on the contrary, correlates poorly and negatively with S^w function ($r = -0.6479$). A closer inspection of the data revealed, however, that they were made up of two distinctive sets. The first covers the lower range of S^w values ($S^w = 1.3398 - 1.4641$) yielding a negative slope (-71.5611) and lower correlation coefficient ($r = -0.8692$). The second set gave the line with a positive slope (84.6404) and very high correlation coefficient ($r = 0.9338$) in the higher range of S^w values ($S^w = 1.4881 - 1.6202$). This finding suggests that the method is more suitable for the molecules with higher S values.

Regression line in Figure 4 clearly shows that R-sided conformers are less stable than their H-sided analogs due to higher »conformational crowding« (*i.e.* higher S^w). Such a good result can be obviously attributed to the large difference between conformers both in energy (up to 27.8 kJ mol^{-1}) and sterical function ($\Delta S^w = -0.0170 - 0.0562$) The R-sided and H-sided conformers of the MDL isomer differed less ($\Delta V < 15$ kJ mol^{-1}, $\Delta S^w = -0.0005 - 0.0408$) and yielded a lower correlation coefficient ($r = 0.8656$).
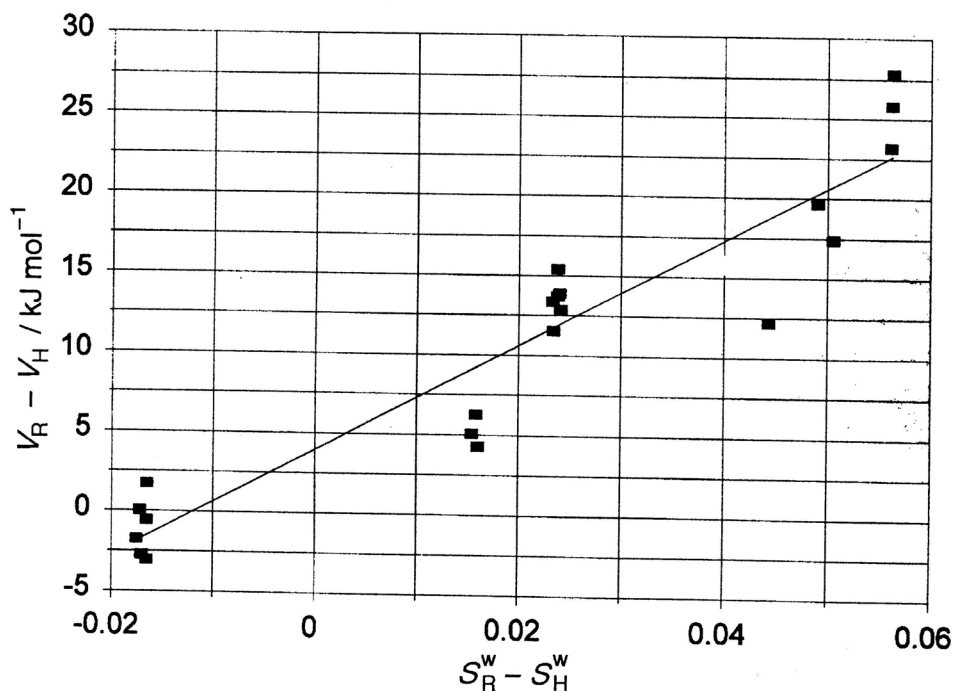

Figure 4. Regression line of the energy difference between the conformers of R-sided and H-sided isomers of aquabis(L-N,N-dimethylvalinato)copper(II). Slope = 332.16 (S.E. = 25.60), intercept = 3.969 (S.E. = 0.833), $r = 0.9479$.

CONCLUSION

From the presented examples it can be concluded that the method of overlapping spheres has the following characteristics:

(1) It is not very sensitive to the molecular geometry; hence molecular energy is not very dependent on atomic coordinates (as in molecular mechanics calculations) but rather on the general shape of the molecule (conformation).

(2) The method is not strongly dependent on the geometrical parameters which define the centre of the interacting sphere (coordinate, radius).

(3) The method is more sensitive to molecules which differ more in sterical strain and less in geometry (molecular topology). It seems that no very reliable forecast can be made of the energy difference between the conformers less than 3–5 kJ mol^{-1} .

In spite of the fact that the method was developed and checked on a limited class of compounds, I hope that the approach of overlapping spheres could be applied to other compounds, not necessarily the coordination ones. For this purpose it is necessary to propose a more general method, which should be the aim of my further research.

REFERENCES

1. A. E. Howard and P. A. Kollman, *J. Med. Chem.* **31** (1988) 1669–1675.
2. A. R. Leach and K. Prout, *J. Comput. Chem.* **11** (1990) 1193–1205.
3. M. Vasquez and H. A. Scheraga, *Biopolymers* **24** (1985) 1437–1447.
4. M. Saunders, *J. Am. Chem. Soc.* **109** (1987) 3150–3152.
5. S. R. Wilson and W. Cui, *Biopolymers* **29** (1990) 225–235.
6. B. A. Berg, *Nature* **361** (1993) 708–710.
7. A. Smellie, S. L. Teig, and P. Towbin, *J. Comput. Chem.* **16** (1995) 171–187.
8. M. Lipton and C. Still, *J. Comput. Chem.* **9** (1988) 343–355.
9. Y. C. Martin and T. Lin, *Three-dimensional quantitative structure-activity relationships: D2 dopamine agonists as an example*, in: C. G. Wermuth (Ed.), *The Practice of Medical Chemistry*, Academic Press, New York, 1996, pp. 459–483.
10. M. J. J. Blommers, C. B. Lucasius, G. Keteman, and R. Kaptein, *Biopolymers* **32** (1992) 45–52.
11. G. N. Ramachandran, *Struct. Chem. Mol. Biol.* (1968) 77–87.
12. B. Kaitner, G. Ferguson, N. Paulić, and N. Raos, *J. Coord. Chem.* **30** (1993) 233–244.
13. B. Kaitner, N. Paulić, and N. Raos, *J. Coord. Chem.* **25** (1992) 337–347.
14. B. Kaitner, E. Meštrović, N. Paulić, and N. Raos, *J. Coord. Chem.* **34** (1995) 55–66.
15. B. Kaitner, G. Pavlović, N. Paulić, and N. Raos, *J. Coord. Chem.* **36** (1995) 327–338.
16. B. Kaitner, G. Ferguson, N. Paulić, and N. Raos, *J. Coord. Chem.* **26** (1992) 95–115.
17. B. Kaitner, G. Pavlović, N. Paulić, and N. Raos, *J. Coord. Chem.*, in press.
18. K. D. Gibson and H. A. Scheraga, *Proc. Natl. Acad. Sci. USA* **58** (1967) 420–427.

19. A. J. Hopfinger, *Conformational Properties of Macromolecules,* Academic Press, New York, 1973.
20. N. Raos and Vl. Simeon, *J. Inorg. Biochem.* **18** (1983) 133–151.
21. A. J. Hopfinger, *J. Am. Chem. Soc.* **102** (1980) 7196–7210.
22. N. Raos and N. Paulić, *J. Coord. Chem.* **31** (1994) 181–190.
23. B. Kaitner, N. Paulić, and N. Raos, *J. Coord. Chem.* **22** (1991) 269–279.
24. V. A. Davankov, S. V. Rogozhin, A. A. Kurganov, and Ya. Zhuchkova, *J. Inorg. Nucl. Chem.* **37** (1975) 369–374.
25. N. Raos and Vl. Simeon, *Croat. Chem. Acta* **56** (1983) 79–85.
26. N. Raos and Vl. Simeon, *Croat. Chem. Acta* **58** (1985) 127–132.
27. J. Sabolović and N. Raos, *Polyhedron* **9** (1990) 1277–1286.
28. J. Sabolović and Kj. Rasmussen, *Inorg. Chem.* **34** (1995) 1221–1232.
29. J. Sabolović, N. Raos, and Kj. Rasmussen, *Croat. Chem. Acta* **62** (1989) 495–503.

SAŽETAK

Procjena konformacijske energije kompleksnih spojeva upotrebom modela preklapanja kugli

Nenad Raos

Nova metoda za procjenu konformacijske energije temelji se na pretpostavci da je sterički napon proporcionalan ispuni volumena (definiranog kuglom radiusa R_{vi}) van der Waalsovim sferama okolnih atoma. Metoda je iskušana na planarnim bis- i aquabis-kompleksima dvovalentnog bakra s N-alkiliranim aminokiselinama, dajući korelacijski koeficient između konformacijske energije i steričkih parametara maksimalne vrijednosti $r = 0{,}95$. Pokazalo se da predložena metoda ne ovisi mnogo o točnoj geometriji molekule ili postupku računanja, no čini se da nije dovoljno pouzdana za male razlike u energiji medu konformerima (< 3–5 kJ mol^{-1}). Stoga bi se njezina buduća primjena mogla vidjeti prvenstveno kao metode za eliminaciju konformacija visoke energije.