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Application of Overlapping Spheres Method for Low-energy Conformation Search to Coordination Compounds: Conformational Analysis of Copper(II) Complexes with 1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-hydroxymethylcyclopropane-1-carboxylic Acids

Nenad Raos and Lora Žuža-Mak*

Institute for Medical Research and Occupational Health, Ksaverska c. 2, P. O. Box 291, 10001 Zagreb, Croatia

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The overlapping spheres (OS) method, based on minimization of the overlapping volume of the central sphere and the van der Waals volumes of neighbouring atoms, was applied to copper(II) mono- and bis-complexes with 1-[*N*-(*tert*-butoxycarbonyl)amino]-2-hydroxymethylcyclopropane-1-carboxylic acid, *N*-Boc-ACC-OH, in the quest for low-energy conformations. The central sphere was situated in the geometrical centre of one kind of molecular fragments in the case of mono-complexes, and three kinds of molecular fragments in the case of bis-complexes; the radius of the sphere varied from 0.3 to 0.6 nm. Altogether 168 and 112 conformations of (*SS*)- and (*SR*)-isomers of mono-complex were obtained, respectively. The conformation with the lowest energy, obtained by the OS method, had the energy only 0.8 kJ mol^{-1} higher than the global minimum. By applying the OS method to bis-complexes of *N*-Boc-ACC-OH, a drop in the conformational energy up to 60 kJ mol^{-1} was achieved in one cycle of optimization.

Key words: copper(II) complexes, amino acids, 1-aminocyclopropane-1-carboxylic acid, overlapping spheres, conformational analysis, global optimization.

* Author to whom correspondence should be addressed. (E-mail: raos@mimi.imi.hr)

INTRODUCTION

There are many methods aimed at searching for low-energy conformations,[1,2] commencing from the simple constructions of presumably low-energy conformations from molecular fragments (subconformations)[3–5] to highly sophisticated methods such as simulated annealing,[6] »hypersurface deformation« techniques,[7] and genetic algorithms.[8] In spite of their diversity and the efforts of many prominent researches over several decades, the problem is not yet generally solved, for the simple reason that there is no general solution to the problem. All these methods are by their very nature numerical, and thus they cannot be exactly, *i.e.* analytically, proved. Hence, development of new methods for the same purpose is needed, at least to check the validity of other methods.

The overlapping spheres (OS) approach for the search for low-energy conformations[9–12] originates from the methods for the estimation of solvation (hydration) energy based on the concept of overlapping sterical volume.[13–15] Later, a model of overlapping sterical volume was applied in QSAR analysis,[16] and more recently a sort of OS method was developed in an attempt to construct a three-dimensional structure of molecules from their graphs (*i.e.*, constitutional formulas).[17–19]

Despite the diversity of these methods, both in their mathematical form and applications, all the methods estimate the volume formed by the penetration of spheres (van der Waals volumes of atoms, or spheres constructed around an atom or group of atoms) one into the other. In the OS model, aimed at the search for low-energy conformations, the central sphere is formed around specific sites in a molecule: apical position(s) in a coordination compound molecule,[9] geometrical centre of a molecule,[10] or the centre of a molecular fragment.[12] In the iterative version of the OS model,[10,12] the minimum overlap between the central sphere and the van der Waals spheres of the neighbouring atoms is searched for using the steepest-descent method of gradient minimization (see Methods).

The OS method proved to be very efficient for unbranched alkanes,[10] and yielded fairy good results for their branched and cyclic counterparts, as well as for copper(II) mono-complexes with amino-acid derivatives.[12] But, the results presented in the mentioned papers show that, in spite of the simplicity of the OS method, there is neither a simple nor general rule that could guarantee the success of the search for low-energy conformations (however, rules for molecule fragmentation along the longest chain, or for choosing the maximum reasonable value of the central sphere radius, generally hold). Hence, the principal aim of this work is to check and develop the OS method for more complex structures, which we found within the realm of the chemistry of coordination compounds. For this purpose, we chose the mono- and bis-complexes of two diastereomers, (1*S*,2*R*) and (1*S*,2*S*), of heavily branched 1-[*N*-(*tert*-butoxycarbonyl)amino]-2-hydroxymethylcyclopropane-1-carboxylic acid, *N*-Boc-ACC-OH.[20] Moreover, there is a pure chemical interest in these complexes: the parent compound, 1-aminocyclopropane-1-carboxylic acid (ACC),[21–23] is a precursor of the plant hormone ethene (»ethylene«), and the copper(II) complexes of the title compound were recently investigated by UV-Vis spectroscopy, revealing the possibility of enantioselectivity effect.[24] For these reasons, it is of interest to make a conformational analysis of these coordination compounds, as detailed as found appropriate.

METHODS

The OS approach is based on the evaluation of the function:[14]

$$v^* = \sum_j v_j (S_v \cap s_j) \tag{1}$$

where v^* is the overlapping volume of the central sphere S_v, with radius R_v, and volumes of the van der Waals spheres s_j of neighbouring atoms. The central sphere is positioned in the geometrical centre of the molecular fragment defined by the postions of the respective atoms. In all calculations, only one v^* function was evaluated per molecule.

The total energy of the molecule is defined as:

$$V_{os} = kv^* + V_b + V_\theta + V_\chi + V\varphi \tag{2}$$

where V_b, V_θ and V_χ are bonding, bond angle bending and out-of-plane potential, respectively, whereas kv^* is the potential dependent on the overlapping sphere volume. Potentials V_b, V_θ, and V_χ were added to fix the overall geometry of the molecule during the steepest-descent minimization. The same holds for the torsional potential $V\varphi$ (the third term in Eq. 3), but it was defined only for two torsional angles per chelate ring – its purpose is to prevent the change of absolute configuration of atoms C1 (C^α) and C2 (C^β) during the course of minimization (see Results and Discussion).

The parameter k (Eq. 2) was taken to have an arbitrary value 21 MJ mol^{-1} nm^{-3}, whereas the other parameters had the same value as in molecular-mechanics calculations, the sole exception being the angles around copper which were taken to be stronger than usual ($k_{\text{N-M-O}} = k_{\text{N-M-X}} = k_{\text{O-M-X}} =$ 97.784; *c.f.* force field FF1).[25,26] After 1000 steepest descent iterations on the intitial (»seed«) conformation, the mean atomic gradient dropped typically from 0.9–1.2 to 0.1–0.2 kJ mol^{-1} pm^{-1} (final results were not altered by further minimization). Usually, a heavily distorted structure was obtained, which was further subjected to the regular molecular-mechanics procedure. Full description of the model as well as its parametrization are given elsewhere.[12]

Molecular-mechanics Step

The conformational potential (or strain energy) was calculated from the general equation:

$$V_\mathrm{T} = \tfrac{1}{2}\sum_i k_{\mathrm{b},i}(b_i - b_{\mathrm{o},i})^2 + \tfrac{1}{2}\sum_j k_\theta\,(\theta_j - \theta_{\mathrm{o},j})^2 + \tfrac{1}{2}\sum_k V_{n,k}(1 \pm \cos n_k\varphi_k) + $$
$$+ \sum_l \left[A_l \exp(-Br_l) - C_l r_l^{-6}\right] + \tfrac{1}{2}\sum_m k_\chi\,\chi_m{}^2 \qquad (3)$$

where b, θ, φ, and χ stand for bond lengths, bond angles, torsion and out-of- plane angles, respectively; r is a non-bonded distance, k_b is an empirical parameter for bond stretching and k_θ for valence angle bending; b_o and θ_o are the equilibrium bond and valence angle values, respectively. Torsion interactions were determined with parameters V_n and n (height and multiplicity of torsional barrier, respectively) and non-bonded interactions were computed from the Buckingham function with parameters A, B, and C. In addition, the out-of-plane deformation potential (k_χ = 100 kcal mol^{-1} rad^{-2}) for angle defining with four atoms (O–CO–N(C) groups) was also calculated (1 cal = 4.184 J). Other parameters for molecular-mechanics calculations are presented elsewhere.[25,26]

All calculations were performed using the program developed by Kj. Rasmussen and co-workers,[27–29] which was modified to deal with function (2).

RESULTS AND DISCUSSION

Conformational Analysis of the Monoligand Complex

The ligand, 1-[*N*-(*tert*-butoxycarbonyl)amino]-2-hydroxymethylcyclopropane-1-carboxylic acid (*N*-Boc-ACC-OH), has two chiral centres (on C^α and C^β atoms), and since the new chiral centre was formed on nitrogen by its coordination to copper(II), mono-complex of *N*-Boc-ACC-OH appeared in the form of four enantiomeric pairs (Figure 1). But, chirality due to nitrogen coordination is easily convertible because of the well-known kinetic flexibility of copper(II) compounds, which means that only two out of four enantiomeric pairs, (*SS*)/(*RR*) and (*SR*)/(*RS*), have to be treated separately.

From the viewpoint of conformational analysis, mono-complexes of *N*-Boc-ACC-OH with copper(II) have two chelate ring conformations (C^β-*exo* and C^β-*endo*), nine conformations defined by the side chain (C^β–CH_2–OH) and an undefined number of conformations of the Boc chain bonded to nitrogen (Figure 2). By changing the torsion angles (φ_1, φ_2 for 15°, and φ_3, φ_4 for 120°, see Supplementary Materials), followed by minimization of conformational energy, we obtained altogether 100 and 164 conformers of isomer (*SR*) and (*SS*), respectively (Tables V and VI)*. The substantially smaller number of conformers of (*SR*)-isomers is due to the high sterical strain in the molecules

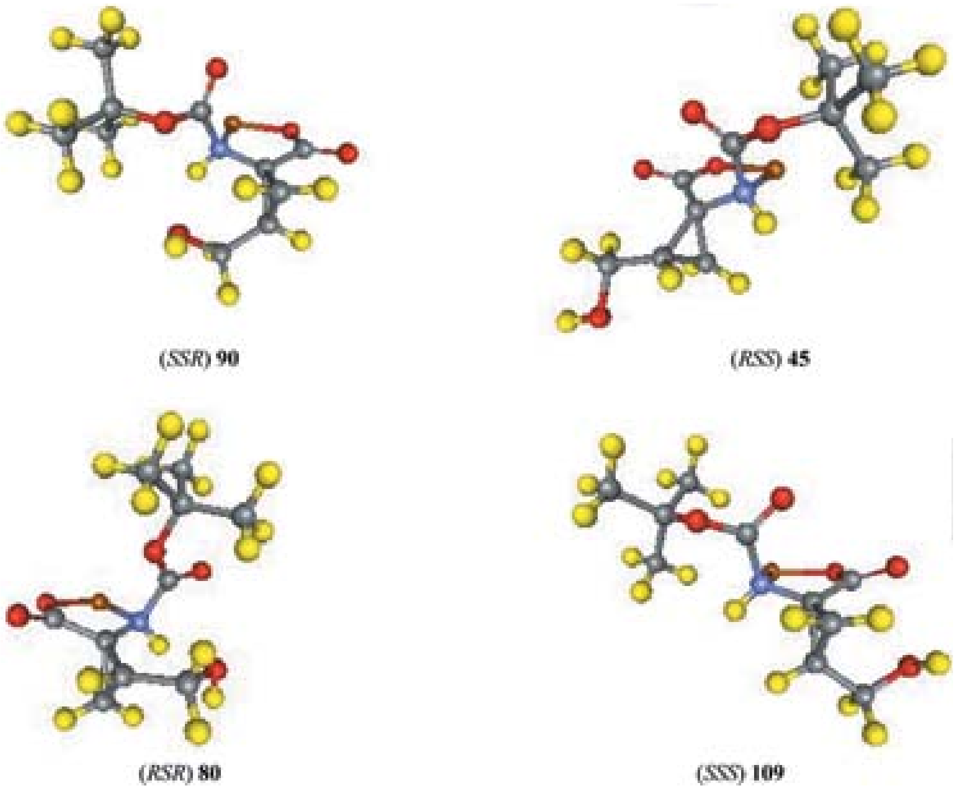


Figure 1. The four high-energy conformations of the four isomes of *N*-Boc-ACC-OH mono-complexes with copper(II), see Tables V and VI.*

of (*SSR*)-isomers with C^{β}-*exo* conformations and (*RSR*)-isomers with C^{β}-*endo* conformations of the chelate ring, which makes only two of such conformers possible (No. 11 and 56, Table V). The distincition between (*SS*)- and (*SR*)-isomers is not so pronounced with respect to the difference in energy of their lowest conformations (No. 100, Table V; No. 55, Table VI), which differ by 3.9 kJ mol^{-1}, but the highest conformer (No. 131, Table VI) of isomer (*SS*) has energy 53.5 kJ mol^{-1} above the global minimum, in contrast to the highest conformer of isomer (*SR*) with the energy of 33.3 kJ mol^{-1} above the global minimum (No. 56, Table V).

* Due to large volume of the data the Tables V and VI are given in the Supplementary Materials. This material may be found at the www under http:// pubwww.srce.hr/ccacaa or will be aviable on request from authors.

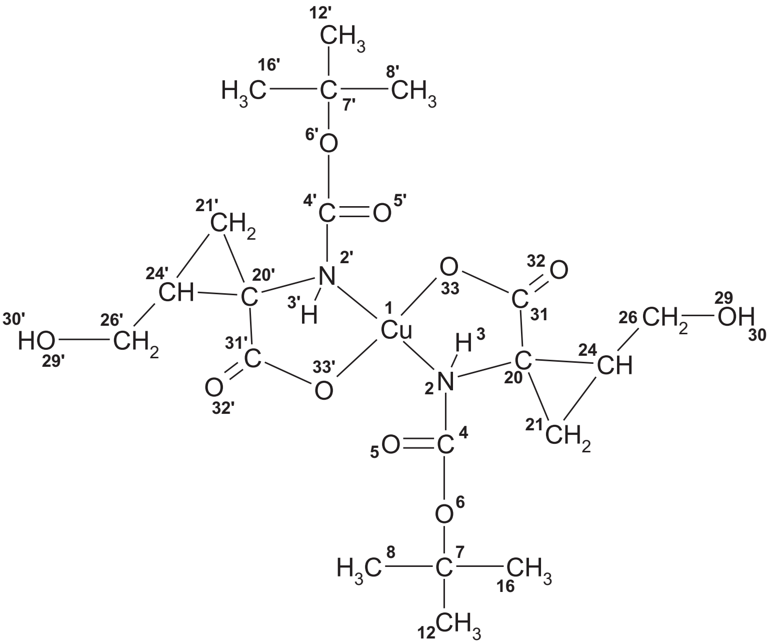


Figure 2. Numbering scheme of the bis-complex of the title ligand, (*N*-Boc-ACC-OH)$_2$Cu.

The first attempts to apply the method of overlapping spheres to the mono-complexes of *N*-Boc-ACC-OH with copper(II) did not prove entirely successful, since the change in chirality on C^{β} took place, and therefore the conformer of the (*SR*)-complex converted to the conformer of (*SS*)-complex, and *vice versa* (Figure 3). To solve this problem, an additional torsion potential was introduced; it was defined by two torsion angles (C20–H25–C26–C21 and C24–C31–N2–C21, V_n = 50 kcal mol^{-1}, n = 4; *c.f.* Eqs. (2) and (3), and Figure 2), aimed to prevent the movement of methoxy group and H25 atom through the cyclopropane ring plane.

It was found that the best fragmentation of molecules for finding the low-energy conformations by the OS method was obtained by choosing the longest and the most flexible chain.[12] The longest chain in the molecule of (*N*-Boc-ACC-OH)Cu(II) has nine chain atoms and can be defined by sequence C(8,12, or 16)–C7–O6–C4–N2–C20–C24–C26–O29, according to the numbering scheme in Figure 2. As the *tert*-butyl end of the chain can be defined by three atoms (8, 12, or 16), we proposed three analogous fragmentations, denoted as 1, 2, and 3 (Table I). It could be seen easily that these fragmentations frequently led to the same results, at least in the first steps of the OS procedure.

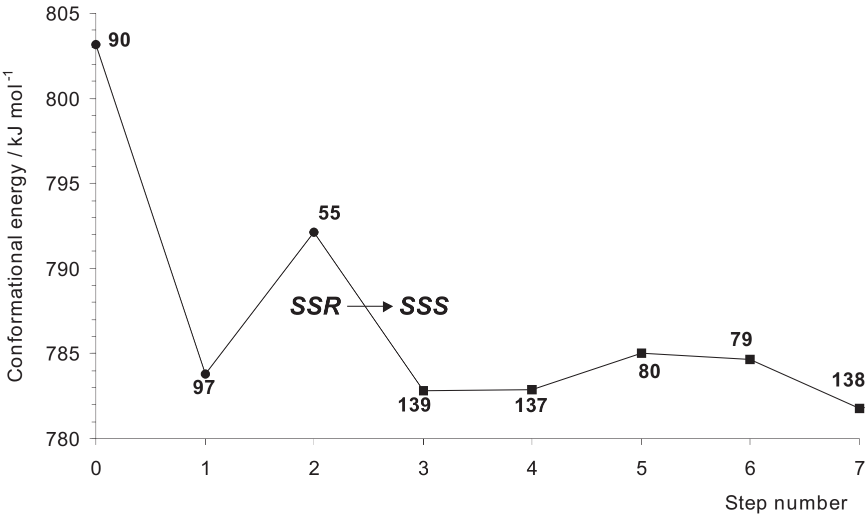


Figure 3. Plot of the OS run on *N*-Boc-ACC-OH mono-complex with copper(II) without the constraint aimed to prevent the change of configuration on the C^{β} atom. Conformations of (*SSR*)- and (*SSS*)-isomers are marked with a circle and square, respectively; numbers denote conformations in Tables V and VI. Run-stream (fragmentations as in Table I; R_v /nm): 1(0.3), 1(0.4), 1(0.5), 1(0.3), 2(0.4), 2(0.5), 2(0.3).

To check our method and to apply it in a systematic way, we chose eight »seed« conformations, taking two »seeds« with different chalate ring conformations for each of the four isomers (Table I). It is interesting to note that the conformation with the lowest energy was usually obtained in the first or the second step; in spite of an occasional rise of the conformational energy in the course of running the OS method, these jumps were usually a few kJ mol^{-1}. The maximal increase of conformational energy was 8.4 kJ mol^{-1} (conformation 57), but such a high rise of energy usully happened after reaching the lowest conformation. In contrast to these findings, the drop of the conformational energy was in the range from 10.5 (conformation 35) to 25.1 (conformation 89) kJ mol^{-1}. The application of the OS potential to the »seed« conformation resulted in the change of all relevant torsion angles, but the conformation of the chelate ring was not changed. The lowest conformers obtained for isomers (*SSR*), (*RSR*), (*RSS*), and (*SSS*) were 0.8, 1.7, 8.8, and 1.1 kJ mol^{-1} above the respective global minimum.

Besides the fact that the OS method generated low-energy conformations, it also generated two conformations of (*SR*)-isomer along with the three conformations of (*SS*)-isomer, which were not obtained by the search of conformational space (these conformers are marked bold in Tables V and VI).

TABLE I

Results of the application of the OS method to mono-complexes of *N*-Boc-ACC-OH with copper(II). The conformer with the lowest energy in a series is typed bold. For the notation of conformers see Tables V and VI, and for the meaning of symbols see Methods.

Step	R_V / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation
(*RSR*)				
0			17.6	80
1	0.3	1	14.0	4
2	**0.4**	**1**	**5.6**	**22**
3	0.5	1	7.7	49
4	0.6	1	7.3	47
5	0.3	1	7.1	52
6	0.6	1	8.3	48
7	0.3	1	7.7	49
0			17.6	80
1	0.3	2	14.0	4
2	**0.4**	**2**	**5.6**	**22**
3	0.5	2	7.7	49
4	0.6	2	7.3	47
5	0.5	2	7.1	52
6	0.6	2	7.3	51
7	0.3	2	7.1	50
8	0.4	2	7.1	52
9	0.6	2	7.3	51
0			17.6	80
1	**0.3**	**3**	**3.7**	**3**
2	0.4	3	4.0	29
3	0.5	3	7.7	49
(*RSR*)				
0			16.2	35
1	0.3	1	12.7	7
2	**0.4**	**1**	**5.6**	**22**
3	0.5	1	7.6	49
0			16.2	35
1	0.3	2	14.0	4
2	**0.4**	**2**	**5.6**	**22**
3	0.5	2	7.6	49
4	0.6	2	7.3	47
5	0.5	2	7.1	52
6	0.6	2	7.3	51
7	0.3	2	7.1	50
8	0.4	2	7.1	52
9	0.6	2	7.3	51
0			16.2	35
1	0.3	3	12.7	7
2	**0.4**	**3**	**7.6**	**49**
(*SSR*)				
0			21.0	90
1	**0.3**	**1**	**1.6**	**97**
2	0.4	1	9.9	55
0			21.0	90
1	**0.3**	**2**	**1.6**	**97**
2	0.5	2	9.7	53
3	0.6	2	9.9	55
0			21.0	90
1	**0.3**	**3**	**1.6**	**97**
2	0.4	3	9.9	55
3	0.5	3	9.0	60
4	0.5	3	9.1	59
5	0.6	3	9.9	55
6	0.5	3	9.0	60
(*SSR*)				
0			19.2	57
1	**0.3**	**1**	**1.5**	**97**
2	0.4	1	9.9	55
0			19.2	57
1	0.3	2	1.5	97
2	**0.5**	**2**	**0.8**	**102**
0			19.2	57
1	**0.3**	**3**	**1.5**	**97**
2	0.4	3	9.9	55
3	0.5	3	9.0	60
4	0.6	3	9.9	55
(*RSS*)				
0			30.4	45
1	**0.3**	**1**	**16.1**	**13**
2	0.4	1	21.8	26

TABLE I (cont.)

Step	R_V / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation
3	0.5	1	19.8	67
4	0.6	1	22.3	47
5	0.3	1	20.3	27
6	0.4	1	19.5	66
7	0.3	1	17.8	63
8	0.5	1	22.3	47
0			30.4	45
1	**0.3**	**2**	**14.9**	**149**
2	0.4	2	19.3	62
3	0.5	2	22.3	47
4	0.3	2	22.0	35
5	0.5	2	22.3	47
0			30.4	45
1	0.3	3	18.3	10
2	0.4	3	22.0	35
3	0.5	3	22.3	47
4	0.3	3	20.3	27
5	0.5	3	19.8	67
6	**0.3**	**3**	**17.8**	**63**
7	0.4	3	19.5	66
8	0.5	3	19.8	67
9	**0.3**	**3**	**17.8**	**63**
(*RSS*)				
0			29.8	40
1	**0.3**	**1**	**17.3**	**12**
2	0.4	1	19.3	62
3	0.5	1	22.3	47
4	0.3	1	20.5	27
5	0.5	1	19.8	67
6	0.3	1	17.8	63
7	0.5	1	22.3	47
0			29.8	40
1	0.3	2	19.3	62
2	0.5	2	22.3	47
3	0.3	2	20.5	27
4	0.4	2	19.5	66
5	0.5	2	22.3	47
6	0.3	2	17.8	63
7	0.4	2	19.5	66
8	0.5	2	21.6	28
9	0.6	2	22.3	47
10	**0.3**	**2**	**16.0**	**13**
11	0.4	2	21.6	26
12	0.5	2	19.8	67
13	0.3	2	17.8	63
0			29.8	40
1	**0.3**	**3**	**17.3**	**12**
2	0.4	3	21.6	26
3	0.5	3	19.8	67
4	0.3	3	17.8	63
5	0.5	3	19.8	67
(*SSS*)				
0			29.0	109
1	0.3	1	4.7	137
2	0.4	1	6.8	80
3	0.5	1	6.4	79
4	0.3	1	5.0	75
5	**0.4**	**1**	**4.4**	**142**
6	0.5	1	4.7	143
7	0.4	1	5.2	141
8	0.5	1	4.7	143
9	0.3	1	5.0	75
0			29.0	109
1	0.3	2	16.9	160
2	**0.4**	**2**	**6.2**	**81**
3	0.5	2	6.4	79
4	0.4	2	6.8	80
5	0.5	2	6.4	79
0			29.0	109
1	0.3	3	4.7	137
2	0.5	3	4.6	139
3	0.6	3	6.8	105
4	0.3	3	3.6	138
5	0.6	3	4.7	143
6	**0.3**	**3**	**4.4**	**142**
7	0.5	3	4.7	143
(*SSS*)				
0			26.2	89
1	0.3	1	4.6	137
2	0.4	1	6.4	74
3	0.5	1	6.1	76
4	0.3	1	6.4	74
5	0.4	1	6.2	81
6	0.5	1	6.4	79

TABLE I (cont.)

Step	R_V / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation	Step	R_V / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation
7	0.6	1	6.1	76	4	0.3	2	5.0	75
8	0.3	1	5.0	75	5	0.5	2	6.1	76
9	**0.4**	**1**	**4.4**	**142**	6	0.6	2	6.4	79
10	0.5	1	4.7	143	7	0.4	2	5.2	141
11	0.4	1	5.2	141					
12	0.5	1	4.7	143	0			26.2	89
13	0.3	1	5.0	75	1	0.3	3	4.6	137
					2	0.4	3	7.0	80
0			26.2	89	**3**	**0.5**	**3**	**1.1**	**164**
1	0.3	2	20.5	140	4	0.6	3	6.4	79
2	**0.4**	**2**	**4.4**	**142**	5	0.4	3	7.0	80
3	0.5	2	4.7	143					

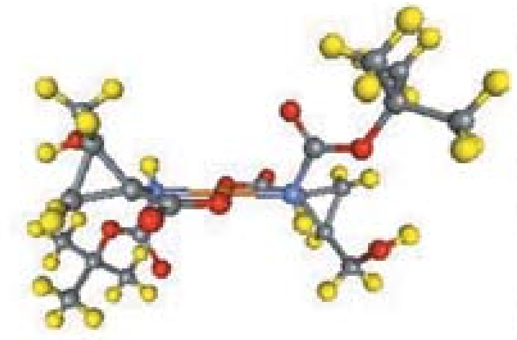
[a]Fragments: C(n)H_3–C(7)–O(6)–C(4)O–N(2)H–C(20)H–C(24)H–C(26)H_2–O(29)H, n = 8 (frag. 1), 12 (frag. 2), 16 (frag. 3). For numbering of atoms see Figure 2.

Conformational Analysis of the Bis-Complex of N*-Boc-ACC-OH*

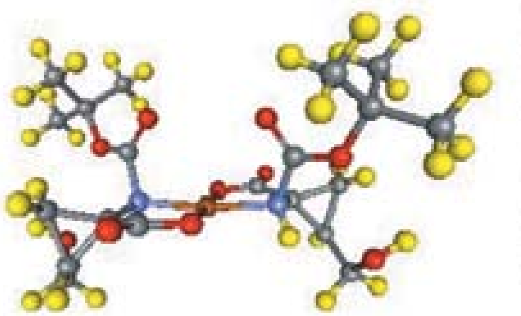
As conformations of bis-complexes of *N*-Boc-ACC-OH can be constructed by combining the conformations of its mono-complexes, it is not hard to calculate the number of conformers of *trans*-Cu(SS)$_2$ and *trans*-Cu(SR)$_2$ from the number of conformations of the constituting chelate rings (12,090 and 5,253, respectively). Moreover, if the bis-complex is formed between two enantiomeric ligands (Figure 4), the same number of conformers of mixed complexes could be proposed. Therefore, the application of a method for the search for low-energy conformations appears in the case of these complexes to be a necessity.

Dealing with the bis-complexes, we applied three fragmentations: the first is the same as for mono-complexes, but with alternation of ring fragmentation during the course of computation (Table II). The second fragmentation runs through the central, *i.e.*, copper(II) atom and includes 11 chain atoms of both chelate rings (Table IV). The third fragmentation is a kind of combination of the previous two fragmentations, namely it includes copper(II) atom and two diverse side chains, each of them belonging to a different chelate ring (Table III).

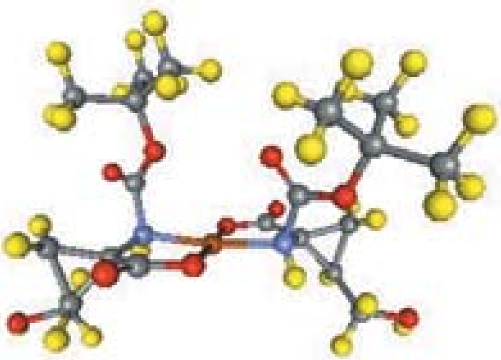
In contrast to the application of the OS procedure to mono-complexes, the lowest conformation in a series was usually obtained after a number of steps (*c.f.* the lowest energy value in the last, 19th, step in the cycle; 160–160, complex (SS)(RR), Table II). The maximal drop of energy in a cycle is also higher than in the case of mono-complex; it amounts to 50.4 kJ mol^{-1}



trans-(*SSR*)(*RRS*) **98-98**



trans-(*SSR*)(*SSR*) **98-98**



trans-(*SSR*)(*SSR*) **95-42**

Figure 4. The »seed« conformation (98–98) of *trans*-$(SSR)_2$ complex of *N*-Boc-ACC-OH with copper(II), its diastereomer, *trans*-(*SSR*)(*RRS*), with the same conformation of chelate rings (98–98), and the conformation with the lowest energy (95–42) obtained from the »seed« conformation.

TABLE II

Conformations of bis-complexes of *N*-Boc-ACC-OH with copper(II), as obtained by the application of the OS method. For notation of conformations see Tables V and VI, for the meaning of symbols see Methods. The conformation with the lowest energy in a series is typed bold.

Step	R_v / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation
trans-(*SR*)(*RS*)				
0	–	–	1579.7	98–98
1	0.3	1	1567.2	99–95
2	0.3	4	1567.5	99–97
3	0.5	3	1559.0	97–97
4	0.5	6	1557.1	97–102
5	0.6	1	1558.5	97–60
6	0.6	4	1558.6	55–101
7	0.3	5	1558.7	55–102
8	0.4	6	1558.4	53–102
9	0.5	1	1561.1	97–102
10	0.5	4	1559.5	97–101
11	**0.6**	**5**	**1553.9**	**42–102**
12	0.3	6	1556.6	42–102
13	0.4	4	1558.5	55–102
14	0.5	2	1561.0	97–102
15	0.5	5	1559.5	97–101
16	0.6	3	1561.2	8–100
17	0.6	6	1554.3	40–101
0	–	–	1588.9	80–80
1	0.3	1	1584.7	4–80
2	0.3	4	1572.2	4–103
3	0.5	3	1572.6	4–21
4	0.5	6	1572.2	4–103
5	0.6	4	1574.2	105–1
6	0.3	2	1570.2	106–1
7	0.3	5	1570.4	106–3
8	0.4	3	1576.3	107–3
9	0.5	1	1560.6	52–2
10	**0.5**	**4**	**1559.6**	**27–1**
11	0.3	3	1560.0	29–1
trans-(*SS*)(*RR*)				
0	–	–	1579.8	160–160
1	0.3	1	1547.3	142–142
2	0.3	4	1548.1	81–155
3	0.4	5	1549.4	81–138
4	0.5	6	1548.3	79–139
5	0.6	1	1546.7	156–139
6	0.6	4	1546.9	156–156
7	0.3	2	1546.8	137–156
8	0.3	5	1545.9	137–137
9	0.4	3	1545.8	137–139
10	0.4	6	1548.4	76–142
11	0.5	1	1546.4	139–105
12	0.3	3	1546.6	154–143
13	0.3	6	1547.6	139–24
14	0.4	4	1546.3	137–137
15	0.4	1	1555.2	137–155
16	0.5	5	1545.4	139–139
17	0.5	2	1547.3	139–138
18	0.6	3	1546.7	156–139
19	**0.6**	**6**	**1545.1**	**139–139**
0	–	–	1582.9	11–11
1	0.3	1	1582.6	10–11
2	0.3	4	1582.3	10–10
3	0.4	2	1582.8	35–10
4	0.5	3	1583.2	47–9
5	0.5	6	1583.4	47–11
6	0.6	1	1580.0	47–65
7	0.6	4	1578.9	65–10
8	0.3	2	1578.7	66–10
9	0.4	3	1579.5	66–34
10	0.4	6	1579.4	66–35
11	0.5	1	1579.8	67–34
12	0.5	4	1579.8	65–47
13	0.6	2	1579.8	47–65
14	0.6	5	1575.7	65–67
15	0.3	3	1575.5	66–67
16	**0.4**	**4**	**1575.2**	**66–66**
17	0.5	2	1575.7	67–65
18	0.5	5	1575.7	65–67
19	0.6	3	1578.9	10–65
trans-(*SR*)(*SR*)				
0	–	–	1579.1	98–98

TABLE II (cont.)

Step	R_v nm	Fragment[a]	V_T kJ mol^{-1}	Conformation
1	0.3	1	1577.4	99–98
2	0.3	4	1574.5	99–99
3	0.5	3	1566.2	113–99
4	0.5	6	1557.8	113–113
5	0.6	4	1554.4	42–97
6	0.4	3	1557.8	113–113
7	**0.6**	**2**	**1554.2**	**95–42**
8	0.3	6	1557.5	53–97
9	0.5	2	1557.8	113–113
10	0.4	1	1557.8	113–97
11	0.5	5	1555.9	95–102
12	0.6	3	1556.8	95–102
13	0.6	6	1558.6	55–96
0	–	–	1586.5	80–80
1	0.3	1	1571.1	22–109
2	0.3	4	1566.8	22–108
3	0.4	5	1568.0	104–104
4	0.5	6	1559.4	78–22
5	0.6	4	1559.0	63–81
6	0.3	2	1560.8	3–81
7	0.3	5	1559.4	3–6
8	0.4	3	1559.2	104–6
9	0.4	6	1557.9	104–29
10	0.5	1	1557.2	20–65
11	**0.4**	**1**	**1555.8**	**29–65**
12	0.4	4	1557.1	29–67
13	0.5	2	1571.5	28–105
14	0.5	5	1556.9	68–20
trans-(*SS*)(*SS*)				
0	–	–	1595.9	160–160
1	0.3	1	1555.8	163–163
2	0.3	4	1554.8	163–75
3	**0.4**	**2**	**1545.5**	**142–75**
4	0.4	5	1547.1	79–142
5	0.5	3	1547.5	105–105
6	0.6	4	1548.2	143–164
7	0.3	2	1545.7	75–105
8	0.4	3	1549.8	80–104
9	0.4	6	1548.0	80–141
10	0.5	1	1547.2	105–105
11	0.6	2	1550.0	139–105
12	0.3	3	1549.1	74–104
13	0.3	6	1547.0	50–75
14	0.4	1	1549.9	137–99
15	0.4	4	1549.7	74–102
16	0.5	2	1547.5	105–79
17	0.6	3	1547.2	105–105
18	0.6	6	1547.0	105–139
0	–	–	1605.5	45–45
1	0.3	1	1583.3	35–11
2	0.3	4	1583.0	35–10
3	0.4	5	1581.8	35–35
4	0.5	3	1582.3	47–34
5	0.5	6	1579.0	65–47
6	0.6	1	1583.2	11–34
7	0.6	4	1578.9	65–47
7	0.3	2	1578.7	66–47
8	**0.4**	**6**	**1578.4**	**66–35**
9	0.5	1	1583.3	11–34
10	0.5	4	1578.9	65–47
11	0.6	2	1582.2	47–34
12	0.6	5	1582.2	34–47
13	0.3	3	1582.0	35–47
14	0.3	6	1581.7	35–35
15	0.5	2	1582.2	47–34
16	0.5	5	1578.9	65–47
17	0.6	3	1582.2	47–34
18	0.6	6	1583.4	34–11

[a]Fragments (1)–(3) are equal to respective fragments in Table I, and fragments (4)–(6) are analogous to fragments (1)–(3) but are defined with respect to the opposite chelate ring, see Figure 2.

(160–160, complex (*SS*)(*SS*), Table II) and 60.1 kJ mol^{-1} (45–45, complex (*SS*)(*SS*), Table IV). It is also interesting to note that conformations of both ligands are changed, even in the same step (*c.f.* 80–80, complex (*SR*)(*SR*),

TABLE III

Conformations obtained by the application of the OS method to bis-complexes of *N*-Boc-ACC-OH with copper (II). The lowest conformation in a series is typed bold. For notation of conformations see Tables V and VI, and for the meaning of symbols see Methods.

Step	R_v / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation
trans-(*SR*)(*RS*)				
0	–	–	1579.7	98–98
1	**0.5**	**13**	**1557.1**	**95–95**
0	–	–	1588.9	80–80
1	**0.3**	**14**	**1584.1**	**110–109**
2	**0.4**	**12**	**1584.1**	**108–109**
trans-(*SS*)(*RR*)				
0	–	–	1579.8	160–160
1	0.3	11	1576.6	161–160
2	**0.3**	**14**	**1573.3**	**161–161**
0	–	–	1582.9	11–11
1	0.3	11	1570.0	151–7
2	0.3	14	1571.2	10–8
3	0.4	12	1568.0	10–104
4	**0.4**	**15**	**1559.6**	**7–104**
5	0.5	13	1562.8	8–8
6	0.6	11	1571.5	11–8
7	0.6	14	1563.4	6–8
8	0.3	12	1562.8	8–8
9	**0.3**	**15**	**1559.6**	**7–104**
10	0.4	13	1560.0	8–104
11	0.6	12	1562.4	8–7
12	0.6	15	1571.5	8–11
13	0.3	13	1574.0	168–7
14	0.3	16	1563.0	8–8
15	0.6	16	1571.6	8–11
trans-(*SR*)(*SR*)				
0	–	–	1579.1	98–98
1	0.3	11	1575.9	98–99
2	0.3	14	1572.7	99–99
3	0.4	12	1563.0	43–97
4	0.4	15	1563.6	23–40
5	0.5	16	1556.5	96–96
6	0.6	11	1556.7	96–97
7	0.6	14	1556.6	97–95
8	0.3	12	1561.7	8–97
9	0.3	15	1558.8	8–42
10	0.5	11	1557.7	96–97
11	0.6	12	1555.9	101–95
12	**0.3**	**13**	**1553.7**	**45–97**
13	0.3	16	1557.9	14–42
14	0.4	11	1555.2	26–42
15	0.4	14	1558.5	102–14
16	0.5	15	1559.2	102–9
17	0.6	13	1555.8	96–102
0	–	–	1586.5	80–80
1	0.3	11	1574.7	63–111
2	0.4	12	1558.4	77–86
3	0.4	15	1558.9	78–70
4	**0.5**	**13**	**1556.2**	**68–6**
5	0.5	16	1556.9	86–69
6	0.6	14	1558.1	6–5
7	0.5	11	1557.1	69–6
8	0.5	14	1556.3	6–68
9	0.6	12	1557.3	16–16
10	0.6	15	1559.3	6–1
11	0.4	14	1557.6	6–77
12	0.5	12	1559.9	5–3
trans-(*SS*)(*SS*)				
0	–	–	1595.9	160–160
1	0.3	11	1576.3	161–160
2	0.3	14	1574.7	161–19
3	0.4	12	1543.6	55–48
4	0.6	14	1546.9	154–25
5	0.3	12	1543.5	50–50
6	0.3	15	1543.9	154–50
7	**0.4**	**13**	**1542.6**	**48–155**
8	0.4	16	1543.9	154–50
9	0.6	15	1547.1	154–25
10	0.3	13	1545.8	50–25
11	0.4	11	1546.1	25–137
12	0.4	14	1543.2	49–49
13	0.6	13	1574.1	25–157
14	0.6	16	1574.8	155–167
0	–	–	1605.5	45–45
1	0.3	11	1563.4	99–10
2	0.3	14	1544.3	76–104
3	0.5	13	1561.6	159–103
4	0.5	16	1568.0	1–150
5	0.6	11	1579.2	14–148
6	0.6	14	1567.0	2–150
7	0.3	12	1561.2	99–159

Step	R_v / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation
8	**0.3**	**15**	**1543.3**	**76–76**
9	0.5	11	1559.3	159–98
10	0.5	14	1567.5	1–136
11	0.6	12	1554.3	3–2
12	0.6	15	1554.3	2–3
13	0.3	13	1548.9	3–99
14	0.4	11	1545.4	99–98
15	0.4	14	1545.5	98–99
16	0.5	12	1545.4	99–98
17	0.5	15	1545.5	98–99
18	0.6	13	1553.8	99–2
19	0.6	16	1554.4	2–3

[a]Fragmentation: $C(n)H_3$–C(7')–O(6')–C(4')O–N(2')–Cu–O(33)–C(31)O–C(20)–C(24)H–$C(26)H_2$–O(29)H, *c.f.* Figure 2. Fragments: 11 (n = 8'), 12 (n = 12'), 13 (n = 16'); fragments (14)–(16) are analogous to fragments (11)–(13), but the chelate rings are reverted.

TABLE IV

Conformations of bis-complexes of *N*-Boc-ACC-OH, as obtained by the application of the OS method. The conformation with the lowest energy in a series is typed bold. For notation of conformations see Tables V and VI, for the meaning of symbols see Methods.

Step	R_v / nm	Fragment[a]	V_T / kJ mol^{-1}	Conformation
trans-(*SR*)(*RS*)				
0	–	–	1579.7	98–98
1	**0.6**	**4**	**1557.3**	**96–97**
2	0.4	6	1559.5	97–53
3	**0.6**	**8**	**1557.3**	**97–95**
0	–	–	1588.9	80–80
1	0.5	3	1575.6	80–77
2	**0.6**	**4**	**1561.7**	**1–2**
3	0.6	8	1562.3	2–2
trans-(*SS*)(*RR*)				
0	–	–	1579.8	160–160
1	0.4	2	1547.2	154–32
2	0.5	3	1547.6	154–33
3	0.6	4	1575.9	159–163
4	**0.5**	**7**	**1546.3**	**155–162**
5	0.6	8	1576.7	159–162
0	–	–	1582.9	11–11
1	**0.3**	**1**	**1562.8**	**8–8**
2	0.5	3	1563.0	7–6
3	0.6	4	1572.1	11–6
trans-(*SR*)(*SR*)				
0	–	–	1579.1	98–98
1	0.3	1	1556.4	95–95
2	0.4	2	1555.0	114–41
3	0.5	3	1554.4	97–42
4	0.6	4	1554.0	96–41
5	0.4	6	1554.8	114–41
6	0.5	7	1553.8	7–16
7	**0.6**	**8**	**1553.6**	**96–41**
0	–	–	1586.5	80–80
1	0.5	3	1589.7	112–112
2	**0.6**	**4**	**1560.8**	**1–1**
trans-(*SS*)(*SS*)				
0	–	–	1595.9	160–160
1	0.3	1	1566.7	60–54
2	**0.6**	**4**	**1543.5**	**163–54**
3	0.5	7	1545.1	162–53
0	–	–	1605.5	45–45
1	0.3	1	1567.9	143–104
2	**0.4**	**2**	**1545.4**	**104–104**
3	0.5	3	1547.2	98–98
4	0.6	4	1559.4	98–159
5	**0.3**	**5**	**1545.4**	**98–99**
6	0.5	7	1547.4	98–98
7	0.6	8	1576.4	149–150
8	**0.3**	**9**	**1545.4**	**98–99**

[a]Fragmentation: C(n)–C(7)–O(6)–C(4)O–N(2)–Cu–N(2')–C(4')O–O(6')–C(7')–$C(m)H_3$, *c.f.* Figure 2. Fragments: 1 (n = 8, m = 8'), 2 (n = 8, m = 12'), 3 (n = 8, m = 16'), 4 (n = 12, m = 8'), 5 (n = 12, m = 12'), 6 (n = 12, m = 16'), 7 (n = 16, m = 8'), 8 (n = 16, m = 12'), 9 (n = 16, m = 16').

Table IV). Occasionally, a change of the ring conformation (C^{ß}-*exo*/C ^{ß}-*endo*) happens, but only for the second and third fragmentation. This was not observed in the case of mono-complexes.

At first, all the three fragmentations appear equally suitable, but their success depends on the starting point, *i.e.*, »seed« conformation. For conformation 11–11, the fragmentation in Table IV yielded a higher drop in energy (20.1 kJ mol^{-1}) after the first step than fragmentation in Table II on the same conformer after 16 steps (drop of only 7.7 kJ mol^{-1}). But this is not true of conformation 160–160, which in all the three procedures yielded virtually the same drop of conformational energy (~ 50 kJ mol^{-1}) after a few steps.

It has also to be noted that application of the OS method to bis-complexes yielded new conformations of chelate rings: 12 conformations of (*SR*)-isomer (Table V), and one conformation of (*SS*)-isomer (Table VI). Two of these conformations (Nos. 113 and 114, Table V) seem to exist only as a part of bis-complex, since it was not possible to obtain the same conformations of mono-complexes. All this proves that the OS method is able to deal with the molecules of considerable structural complexity.

REFERENCES

1. G. M. Keseru and I. Kolossvary, *Molecular Mechanics and Conformational Analysis in Drug Design*, Blackwell Science, Malden, 1998.
2. D. J. Wales and H. A. Scheraga, *Science* **285** (1999) 1368–1372.
3. A. R. Leach and K. Prout, *J. Comput. Chem.* **11** (1990) 1193–1205.
4. N. Raos and V. Simeon, *Croat. Chem. Acta* **57** (1984) 1217–1224.
5. M. Vasquez and H. A. Scheraga, *Biopolymers* **24** (1985) 1437–1447.
6. S. R. Wilson and W. Cui, *Biopolymers* **29** (1990) 225–235.
7. R. J. Wawak, K. D. Gibson, A. Liwo, and H. A. Scheraga, *Proc. Natl. Acad. Sci. USA* **93** (1996) 1743–1746.
8. M. J. J. Blommers, C. B. Lucasius, G. Kateman, and R. Kaptein, *Biopolymers* **32** (1992) 45–52.
9. N. Raos, *Croat. Chem. Acta* **70** (1997) 913–924.
10. N. Raos, *Croat. Chem. Acta* **72** (1999) 727–736.
11. N. Raos, *Kem. Ind.* **48** (1999) 385–390.
12. N. Raos, *J. Comput. Chem.* **21** (2000) 1353–1360.
13. K. D. Gibson and H. A. Scheraga, *Proc. Natl. Acad. Sci. USA* **58** (1967) 420–427.
14. A. J. Hopfinger, *Conformational Properties of Macromolecules*, Academic Press, New York, 1973.
15. N. Raos and Vl. Simeon, *J. Inorg. Biochem.* **18** (1983) 133–151.
16. A. J. Hopfinger, *J. Am. Chem. Soc.* **102** (1980) 7196–7210.
17. T. Pisanski, B. Plestenjak, and A. Graovac, *Croat. Chem. Acta* **68** (1995) 283–292.
18. T. Pisanski, M. Razinger, and A. Graovac, *Croat. Chem. Acta* **69** (1996) 827–836.
19. A. Graovac, A. Orbanić, and T. Pisanski, *MATCH-Commun. Math. Comput Chem.* **44** (2001) 305–317.

20. M. C. Pirrung, S. E. Dunlop, and U. P. Trinks, *Helv. Chim. Acta* **72** (1989) 1301–1310.
21. Z. Prochazka, *Chem. Listy* **79** (1985) 1042–1053.
22. C. H. Stammer, *Tetrahedron* **46** (1990) 2231–2254.
23. L. Burroughs, *Nature* **179** (1957) 360–361.
24. L. Žuža and N. Raos, 17th Croatian Meeting of Chemists and Chemical Engineers, Osijek June 10–13, 2001. Book of Abstract p. 117.
25. N. Raos, S. R. Niketić, and Vl. Simeon, *J. Inorg. Biochem.* **16** (1982) 1–19.
26. B. Kaitner, N. Paulić, and N. Raos, *J. Coord. Chem.* **22** (1991) 269–279.
27. S. R. Niketić and Kj. Rasmussen, *The Consistent Force Field: A Documentation*, Lecture Notes in Chemistry, Vol. 3, Springer-Verlag, Berlin, 1977.
28. Kj. Rasmussen, *Potential Energy Functions in Conformational Analysis*, Lecture Notes in Chemistry, Vol. 37, Springer-Verlag, Berlin, 1985.
29. Kj. Rasmussen, S. B. Engelsen, J. Fabricius, and B. Rasmussen, *The Consistent Force Field: Development of Potential Energy Functions in Conformational Analysis, Recent Experimental and Computational Advances in Molecular Spectroscopy*, Proceedings of the NATO Advanced Study Institute on MOLECULAR SPECTROSCOPY, Ponta Delgada, Sao Miguel, Acores, Portugal, 1992, R. Fausto (Ed.), NATO ASI Seiries C: Mathematical and Phyisical Sciences, Vol. 406, Kluwer Academic Publishers, Dodrecht, 1993, pp. 381–419.

SAŽETAK

Metoda preklapanja kugli za traženje konformacija niskih energija primijenjena na kompleksnim spojevima: konformacijska analiza kompleksa bakra(II) s 1-[*N*-(*tert*-butoksikarbonil)amino]-2-hidroksimetilciklopropan-1-karboksilnim kiselinama

Nenad Raos i Lora Žuža-Mak

Metodu preklapanja kugli (*overlapping spheres*, OS), utemeljenu na minimalizaciji presjeka volumena središnje kugle i van der Waalsovih volumena susjednih atoma, primijenili smo na bakrove(II) mono- i bis-komplekse 1-[*N*-(*tert*-butoksikarbonil)amino]-2-hidroksimetilciklopropan-1-karboksilne kiseline, *N*-Boc-ACC-OH, da bismo potražili konformacije niskih energija. Kod mono-kompleksa središnja je kugla smještena u geometrijskom središtu jedne vrste molekulskih fragmenata, a kod bis-kompleksa u geometrijskom središtu triju vrsta, dok je radius kugle mijenjan u rasponu od 0,3 do 0,6 nm. Sveukupno je nađeno 168 konformacija izomera (*SS*) i 112 konformacija izomera (*SR*). Konformacija s najnižom energijom dobivena metodom OS ima energiju višu za samo 0,8 kJ mol^{-1} od globalnog minimuma. Primjenom metode OS na bis-komplekse *N*-Boc-ACC-OH tijekom jednog ciklusa optimalizacije postignut je pad konformacijske energije i do 60 kJ mol^{-1}.

Supplementary Materials

TABLE V

Conformations of (*SR*)-isomer of mono-complex of *N*-Boc-ACC-OH with copper(II). V_{T0} = 782.2 kJ mol^{-1} (conformation No. 100)

No[b]	V_T / kJ mol^{-1}	Configu-ration	Torsion angles / ° [a]				
			φ_1	φ_2	φ_3	φ_4	φ_5
1	3.5	RSR	–150.1	–169.0	–66.7	–61.0	31.0
2	4.1	RSR	–150.3	–170.8	–72.2	62.8	30.8
3	3.7	RSR	–150.1	–169.0	–67.4	–179.9	31.0
4	**14.0**	**RSR**	**–150.4**	**–170.7**	**41.2**	**178.8**	**30.6**
5	2.4	RSR	–151.3	–174.2	172.6	61.7	31.2
6	2.1	RSR	–148.3	–176.1	174.0	179.4	31.2
7	**12.7**	**RSR**	**–153.1**	**103.1**	**–66.4**	**180.0**	**31.2**
8	6.8	SSR	–153.2	173.1	–76.2	–61.8	–27.5
9	6.8	SSR	–153.1	173.2	–80.2	61.6	–27.5
10	7.1	SSR	–153.2	173.2	–77.1	–179.5	–27.5
11	31.2	RSR	–156.1	167.5	–35.1	–60.5	–28.9
12	16.1	SSR	–153.8	174.9	25.8	179.5	–25.8
13	5.1	SSR	–153.1	172.9	164.0	–60.8	–28.1
14	6.2	SSR	–153.1	173.2	161.6	60.9	–27.4
15	6.2	SSR	–153.1	173.2	162.3	–179.5	–27.4
16	2.0	RSR	–153.1	176.2	176.0	–59.9	32.1
17	3.6	SSR	–82.7	–172.1	–74.7	–61.7	–21.0
18	3.7	SSR	–82.8	–172.0	–78.6	61.8	–21.2
19	3.8	SSR	–82.7	–172.1	–75.6	–179.6	–21.0
20	5.4	RSR	–98.0	–169.9	–66.1	–61.0	25.9
21	6.1	RSR	–98.0	–170.6	–71.6	62.9	25.5
22	5.6	RSR	–98.1	–169.5	–66.8	–179.9	25.7
23	12.1	SSR	–82.2	–172.9	33.0	179.8	–17.7
24	3.1	SSR	–82.9	–172.2	64.1	–179.5	–21.1
25	2.0	SSR	–82.9	–171.3	165.9	–60.8	–22.0
26	3.2	SSR	–82.9	–172.1	163.6	61.1	–21.1
27	3.4	RSR	–99.4	–174.9	177.3	–59.9	27.4
28	4.4	RSR	–97.0	–172.6	172.5	61.8	25.6
29	4.0	RSR	–94.6	–173.3	173.9	179.2	25.9
30	12.4	RSR	–88.3	–3.3	–61.4	–60.7	28.5
31	13.3	RSR	–88.5	–2.7	–68.7	63.8	27.8
32	12.6	RSR	–88.5	–3.2	–61.6	179.6	28.5
33	11.5	RSR	–89.7	–1.5	179.1	–61.5	28.9
34	15.3	RSR	–103.6	68.0	–63.0	–60.7	28.8
35	16.2	RSR	–103.9	68.3	–70.1	63.3	28.1
36	15.6	RSR	–103.6	68.0	–63.5	179.9	28.8
37	13.9	RSR	–107.4	72.3	175.3	–61.6	28.3
38	15.3	RSR	–103.8	68.3	173.5	62.0	27.7

TABLE V (cont.)

No[b]	V_T / kJ mol^{-1}	Configu-ration	Torsion angles / ° [a]				
			φ_1	φ_2	φ_3	φ_4	φ_5
39	15.0	RSR	–104.2	68.7	173.3	–179.2	27.5
40	2.7	SSR	–37.6	–163.4	–74.8	–61.7	–21.4
41	2.8	SSR	–37.5	–163.2	–78.8	61.8	–21.7
42	2.9	SSR	–37.6	–163.5	–75.6	–179.6	–21.4
43	11.7	SSR	–38.3	–165.5	31.2	179.8	–19.7
44	1.5	SSR	–37.2	–165.2	165.8	–60.8	–22.5
45	2.3	SSR	–37.3	–163.7	163.5	61.1	–21.6
46	2.2	SSR	–37.4	–163.7	164.1	–179.5	–21.5
47	7.3	RSR	–30.1	175.3	–62.7	–60.7	33.0
48	8.3	RSR	–29.7	175.3	–68.7	63.7	32.9
49	7.6	RSR	–30.1	175.4	–63.2	180.0	32.9
50	7.1	RSR	–29.9	175.1	–177.3	–60.1	33.7
51	7.3	RSR	–30.0	175.4	176.8	62.2	32.8
52	7.1	RSR	–30.0	175.5	177.0	–179.5	32.8
53	9.7	SSR	26.8	–175.7	–76.3	–61.9	–28.1
54	9.7	SSR	26.9	–175.7	–80.4	61.6	–28.2
55	9.9	SSR	26.8	–175.7	–77.3	–179.5	–28.1
56	33.3	RSR	24.7	–169.6	–31.2	–60.7	–30.6
57	19.2	SSR	26.9	–176.2	22.6	179.8	–27.1
58	8.0	SSR	26.8	–175.6	163.8	–60.8	–28.6
59	9.1	SSR	26.8	–175.8	161.4	60.9	–28.0
60	9.1	SSR	26.8	–175.8	162.2	–179.4	–28.0
61	17.0	SSR	25.8	102.0	–76.4	–61.9	–27.3
62	5.6	RSR	35.2	163.8	–65.3	–60.9	32.3
63	6.3	RSR	36.0	159.9	–72.0	62.8	31.7
64	5.9	RSR	35.2	163.8	–65.9	–179.9	32.2
65	3.5	RSR	37.7	167.7	174.0	–60.4	31.8
66	4.7	RSR	39.7	152.4	170.4	61.3	30.9
67	4.5	RSR	40.1	154.8	170.6	–178.8	30.8
68	3.2	RSR	94.9	–173.2	179.8	–58.7	29.5
69	3.6	RSR	95.1	–177.8	175.9	61.8	28.0
70	3.4	RSR	92.6	–177.6	177.0	179.8	28.3
71	12.9	SSR	90.3	–0.1	–76.5	–61.9	–24.7
72	12.9	SSR	90.3	0.0	–80.4	61.6	–24.6
73	13.1	SSR	90.4	–0.2	–77.5	–179.6	–24.6
74	11.0	SSR	90.1	0.5	163.2	–61.0	–25.1
75	12.2	SSR	90.2	–0.2	160.5	60.9	–24.4
76	12.3	SSR	90.3	–0.4	160.9	–179.1	–24.2
77	4.1	RSR	91.2	174.9	–62.8	–60.8	28.0
78	5.0	RSR	91.1	177.5	–69.3	63.5	27.7
79	4.4	RSR	91.3	174.9	–63.3	180.0	28.0
80	17.6	RSR	92.9	177.9	48.7	–78.4	26.4

TABLE V (cont.)

No[b]	V_T / kJ mol^{-1}	Configu-ration	Torsion angles / ° [a]				
			φ_1	φ_2	φ_3	φ_4	φ_5
81	3.5	RSR	149.9	–177.7	–62.6	–60.8	32.3
82	4.5	RSR	150.4	–176.9	–68.2	63.8	32.4
83	3.8	RSR	150.0	–177.9	–63.1	180.0	32.3
84	3.8	RSR	149.8	–176.1	–174.3	–57.7	34.2
85	2.9	RSR	150.5	–173.5	179.0	62.0	32.9
86	2.6	RSR	150.8	–172.4	179.8	179.8	33.1
87	10.1	SSR	148.8	–104.4	–74.7	–61.7	–18.6
88	10.2	SSR	148.9	–104.2	–78.6	61.9	–18.9
89	10.3	SSR	148.9	–104.2	–75.4	–179.9	–18.4
90	21.0	SSR	149.1	–103.8	27.6	–78.3	–18.7
91	17.3	SSR	148.7	–104.3	32.0	179.7	–18.2
92	8.7	SSR	148.6	–103.3	166.4	–60.8	–19.9
93	9.7	SSR	148.7	–103.7	163.6	61.1	–18.8
94	9.5	SSR	148.8	–103.2	164.1	–179.3	–18.5
95	1.3	SSR	148.1	173.6	–74.6	–61.7	–19.5
96	1.3	SSR	148.2	173.4	–78.4	61.9	–19.7
97	1.5	SSR	148.1	173.6	–75.3	–179.7	–19.4
98	12.8	SSR	147.7	172.8	25.6	–78.0	–19.4
99	9.6	SSR	147.5	172.9	31.6	179.9	–18.8
100	0.0	SSR	148.3	173.2	166.3	–60.7	–20.8
101	0.9	SSR	148.2	173.5	163.7	61.1	–19.8
102	0.8	SSR	148.2	173.6	164.3	–179.5	–19.7
103	*5.6*	*RSR*	*–98.1*	*106.4*	*–66.8*	*–179.9*	*25.7*
104	*14.6*	*RSR*	*–97.5*	*–173.7*	*43.3*	*–179.9*	*24.6*
105	*21.1*	*RSR*	*–31.2*	*176.6*	*49.8*	*–80.5*	*31.5*
106	*17.3*	*RSR*	*–31.6*	*177.9*	*54.9*	*179.5*	*31.7*
107	*23.5*	*RSR*	*–42.5*	*179.4*	*66.4*	*79.5*	*34.9*
108	*13.2*	*RSR*	*148.3*	*179.1*	*53.5*	*178.5*	*31.1*
109	*17.4*	*RSR*	*148.7*	*–177.3*	*49.7*	*–80.2*	*31.2*
110	*13.9*	*RSR*	*93.4*	*174.4*	*52.4*	*178.6*	*26.8*
111	*19.5*	*RSR*	*140.3*	*–179.9*	*63.0*	*82.7*	*34.3*
112	*18.1*	*RSR*	*–150.2*	*–171.1*	*39.8*	*–78.2*	*31.1*
113[c]	–	*SSR*	*91.4(3)*	*–161.8(3)*	*–76.1(1)*	*–179.5*	*–21.2(1)*
114[c]	–	*SSR*	*94.0(1)*	*–171.4(14)*	*–78.8*	*61.7*	*–20.6*

[a]Torsion angles: φ_1, O6–C4–N2–Cu; φ_2, C7–O6–C4–N2; φ_3, O29–C26–C24–C21; φ_4, H30–O29––C26–C24; φ_5, O32–C31–C20–N2; as denoted in Figure 2.

[b]Conformations obtained by conventional mapping of conformational space are typed in normal, those obtained by the OS procedure on mono-complexes in bold, and the conformers furnished by the OS procedure on bis-complexes are typed in italics.

[c] These conformations are observed only in the form of bis-complex (maximum difference from the mean value is written in parentheses). Taken as mono-complexes, conformations 113 and 114 converged to conformation No. 97 and 96, respectively.

TABLE VI

Conformations of (*SS*)-isomer of mono-complex of *N*-Boc-ACC-OH with copper(II). V_{T0} = 778.2 kJ mol^{-1} (conformation No. 155)

No[b]	V_T / kJ mol^{-1}	Configu-ration	Torsion angles / ° [a]				
			φ_1	φ_2	φ_3	φ_4	φ_5
1	7.0	RSS	–152.9	–177.1	–178.4	–62.1	–32.1
2	6.1	RSS	–153.0	–177.2	–176.3	61.0	–32.2
3	7.1	RSS	–153.0	–177.3	–178.7	–179.9	–32.2
4	24.3	RSS	–154.3	–176.4	–45.3	78.9	–36.8
5	20.7	RSS	–153.5	–177.1	–59.3	179.9	–36.6
6	7.9	RSS	–153.1	–177.1	68.8	–63.4	–32.2
7	6.8	RSS	–153.0	–177.1	60.1	60.5	–32.2
8	7.3	RSS	–152.9	–177.3	60.5	–179.9	–32.2
9	18.5	RSS	–154.4	–172.4	78.5	–61.7	37.4
10	18.3	RSS	–154.4	–172.7	73.6	61.5	37.7
11	18.6	RSS	–154.4	–172.8	74.5	179.6	37.7
12	17.3	RSS	–156.4	–163.8	–161.9	–60.8	36.6
13	16.0	RSS	–154.8	–168.4	–163.9	61.0	36.8
14	17.5	RSS	–155.9	–163.8	–163.0	179.4	36.8
15	3.7	SSS	–152.4	171.3	–175.0	–62.1	–33.3
16	2.6	SSS	–152.4	171.3	–173.1	61.3	–33.2
17	3.7	SSS	–152.4	171.3	–175.4	179.9	–33.3
18	18.9	SSS	–152.4	169.6	–46.0	77.8	–37.1
19	15.8	SSS	–152.4	169.8	–49.0	–179.9	–36.9
20	4.3	SSS	–152.4	171.2	70.1	–63.1	–33.2
21	3.6	SSS	–152.4	171.2	62.9	60.8	–33.3
22	3.9	SSS	–152.4	171.2	63.5	180.0	–33.3
23	2.5	SSS	–85.8	–170.8	–176.6	–62.3	–30.7
24	1.5	SSS	–85.9	–170.9	–174.4	61.3	–30.7
25	2.5	SSS	–85.8	–170.8	–176.9	180.0	–30.7
26	21.6	RSS	–92.5	–179.5	–163.3	–61.1	37.0
27	20.3	RSS	–92.4	–179.5	–164.5	60.9	37.0
28	21.6	RSS	–92.5	–179.7	–164.4	179.5	37.1
29	18.5	SSS	–86.6	–172.1	–45.8	78.2	–34.7
30	15.2	SSS	–86.4	–172.1	–52.8	180.0	–34.6
31	3.1	SSS	–85.8	–170.7	69.1	–63.3	–30.6
32	2.3	SSS	–85.7	–170.7	61.3	60.7	–30.6
33	2.6	SSS	–85.7	–170.8	61.9	180.0	–30.6
34	22.2	RSS	–92.4	–179.9	78.2	–61.7	37.2
35	22.0	RSS	–92.4	–179.9	73.3	61.5	37.5
36	26.2	RSS	–86.8	–8.6	–164.8	61.0	38.1
37	28.0	RSS	–86.9	–8.4	78.2	–61.7	38.2
38	27.8	RSS	–86.9	–8.4	73.2	61.5	38.5
39	28.1	RSS	–86.9	–8.4	74.1	179.6	38.5
40	29.8	RSS	–100.9	64.1	–164.0	–61.2	38.0
41	28.5	RSS	–100.7	63.8	–164.8	61.0	38.0
42	29.7	RSS	–101.0	64.1	–164.7	179.5	38.1

TABLE VI (cont.)

No[b]	V_T / kJ mol^{-1}	Configu-ration	Torsion angles / ° [a]				
			φ_1	φ_2	φ_3	φ_4	φ_5
43	30.3	RSS	–101.1	64.3	78.1	–61.8	38.1
44	30.1	RSS	–101.1	64.2	73.1	61.5	38.4
45	30.4	RSS	–101.1	64.3	74.0	179.6	38.3
46	22.3	RSS	–92.4	110.2	177.8	–62.1	37.5
47	**22.3**	**RSS**	**–92.4**	**180.0**	**74.2**	**179.6**	**37.5**
48	1.8	SSS	–34.1	–164.9	–176.4	–62.3	–31.5
49	0.7	SSS	–34.0	–165.3	–174.2	61.3	–31.5
50	1.7	SSS	–34.1	–164.9	–176.7	180.0	–31.5
51	17.4	SSS	–33.6	–160.1	–46.2	78.2	–35.7
52	14.1	SSS	–33.8	–159.8	–52.4	180.0	–35.5
53	2.3	SSS	–34.3	–164.2	69.3	–63.3	–31.4
54	1.5	SSS	–34.3	–164.0	61.5	60.7	–31.5
55	1.9	SSS	–34.3	–164.1	62.2	180.0	–31.5
56	28.3	SSS	–20.5	–175.8	–165.3	–61.4	40.9
57	27.2	SSS	–20.5	–175.9	–165.8	61.3	40.9
58	28.3	SSS	–20.4	–175.9	–165.8	179.6	40.9
59	28.6	SSS	–20.5	–175.6	77.7	–61.7	40.9
60	28.4	SSS	–20.5	–175.1	72.1	61.3	41.2
61	28.7	SSS	–20.4	–175.4	73.1	179.6	41.2
62	19.1	RSS	–25.1	172.6	–164.2	–61.1	39.2
63	17.8	RSS	–25.1	172.4	–165.1	60.9	39.2
64	19.1	RSS	–25.1	172.6	–165.0	179.5	39.3
65	19.7	RSS	–25.1	172.7	77.8	–61.8	39.3
66	19.5	RSS	–25.1	172.6	72.8	61.5	39.6
67	19.8	RSS	–25.1	172.6	73.7	179.6	39.6
68	40.5	RSS	–6.5	116.3	–45.2	79.3	–37.9
69	22.8	RSS	–1.1	12.8	58.1	–179.8	–31.9
70	23.5	RSS	–2.6	113.7	67.8	–63.8	–32.5
71	22.4	RSS	–1.1	112.8	57.8	60.5	–31.9
72	22.3	RSS	–2.1	111.3	177.1	–179.9	–32.3
73	21.9	RSS	–1.5	110.3	177.9	–62.0	–32.0
74	6.4	SSS	26.7	–175.0	–174.7	–62.1	–33.4
75	5.2	SSS	26.7	–175.0	–172.9	61.3	–33.4
76	6.3	SSS	26.7	–175.0	–175.2	179.9	–33.4
77	21.6	SSS	26.4	–174.5	–45.9	77.7	–37.1
78	18.4	SSS	26.4	–174.5	–48.3	–179.9	–36.9
79	6.6	SSS	26.7	–175.0	63.8	180.0	–33.4
80	7.0	SSS	26.8	–175.0	70.4	–63.1	–33.4
81	6.2	SSS	26.7	–175.0	63.1	60.8	–33.4
82	31.8	RSS	37.9	–21.3	–170.7	67.2	–31.8
83	49.3	RSS	39.1	–19.9	–45.1	79.3	–35.1
84	32.5	RSS	40.9	–19.5	68.1	–63.7	–30.4
85	31.3	RSS	41.6	–19.4	57.8	60.5	–30.1
86	31.7	RSS	41.6	–19.4	58.1	–179.8	–30.1
87	31.7	RSS	40.2	–20.5	174.8	–63.5	–30.6

TABLE VI (cont.)

No[b]	V_T / kJ mol^{-1}	Configu-ration	Torsion angles / ° [a] φ_1	φ_2	φ_3	φ_4	φ_5
88	31.8	RSS	39.5	–20.2	178.2	180.0	–31.1
89	26.2	SSS	23.9	99.2	–48.5	–179.9	–36.6
90	13.9	SSS	24.2	99.6	63.0	60.8	–33.1
91	17.3	RSS	32.6	153.2	–160.4	–60.6	37.7
92	15.7	RSS	30.2	157.7	–164.3	60.8	38.4
93	17.3	RSS	30.7	158.5	–163.3	179.3	38.5
94	18.1	RSS	29.4	164.7	78.0	–61.8	38.8
95	17.9	RSS	29.3	165.0	73.1	61.5	39.1
96	18.2	RSS	29.4	165.0	74.0	179.6	39.1
97	7.1	RSS	31.5	178.3	–178.0	–61.9	–31.4
98	6.1	RSS	31.6	177.3	–178.1	60.3	–30.9
99	7.5	RSS	31.0	178.0	–179.3	–179.9	–31.3
100	25.1	RSS	29.4	179.6	–45.5	79.0	–36.4
101	21.4	RSS	30.3	179.1	–61.8	179.9	–36.0
102	8.6	RSS	30.5	179.0	68.5	–63.5	–31.7
103	7.6	RSS	30.7	179.2	59.8	60.6	–31.6
104	8.0	RSS	30.7	179.4	60.2	–179.9	–31.6
105	**6.8**	**SSS**	**97.6**	**–166.1**	**70.2**	**179.7**	**–31.1**
106	13.1	SSS	104.5	–70.1	–176.3	–62.3	–30.8
107	12.0	SSS	104.4	–69.9	–174.1	61.3	–30.8
108	13.0	SSS	104.5	–70.1	–176.6	180.0	–30.8
109	29.0	SSS	103.7	–69.2	–45.5	78.1	–34.7
110	25.7	SSS	103.8	–69.3	–51.9	180.0	–34.7
111	13.7	SSS	104.6	–70.2	69.3	–63.3	–30.7
112	12.9	SSS	104.6	–70.2	61.6	60.7	–30.7
113	13.2	SSS	104.6	–70.2	62.2	180.0	–30.7
114	10.9	SSS	91.6	4.4	–176.2	–62.2	–30.9
115	9.8	SSS	91.5	4.5	–174.0	61.3	–31.0
116	10.9	SSS	91.6	4.4	–176.5	180.0	–31.0
117	11.5	SSS	91.6	4.4	69.4	–63.3	–30.9
118	10.7	SSS	91.7	4.4	61.7	60.7	–30.9
119	11.0	SSS	91.7	4.4	62.3	180.0	–30.9
120	12.2	SSS	88.7	99.9	–176.5	–62.3	–29.6
121	11.2	SSS	88.7	100.0	–174.3	61.3	–29.7
122	12.2	SSS	88.7	100.0	–176.8	180.0	–29.7
123	52.4	SSS	109.7	97.2	–168.2	–61.7	43.5
124	51.4	SSS	109.2	97.2	–168.1	61.2	43.5
125	52.7	SSS	109.2	97.3	–169.1	179.7	43.5
126	28.1	SSS	88.2	100.5	–45.7	78.2	–33.9
127	24.8	SSS	88.5	100.2	–52.6	180.0	–33.6
128	12.8	SSS	88.7	100.0	69.3	–63.3	–29.6
129	12.0	SSS	88.8	99.9	61.4	60.7	–29.6
130	12.3	SSS	88.8	100.0	62.0	180.0	–29.6
131	53.5	SSS	108.3	97.6	75.4	–62.1	43.4
132	53.0	SSS	108.8	97.6	69.3	61.2	43.5

TABLE VI (cont.)

No[b]	V_T / kJ mol^{-1}	Configuration	Torsion angles / ° [a]				
			φ_1	φ_2	φ_3	φ_4	φ_5
133	53.4	SSS	108.7	97.6	70.0	179.7	43.5
134	18.7	RSS	89.5	164.5	–158.3	–60.2	35.9
135	17.3	RSS	88.0	172.8	–163.9	60.5	37.3
136	19.0	RSS	90.0	168.4	–160.9	179.1	36.8
137	4.7	SSS	97.6	176.2	–176.4	–62.3	–30.1
138	3.7	SSS	97.4	176.3	–174.2	61.3	–30.1
139	4.7	SSS	97.5	176.2	–176.7	180.0	–30.1
140	**20.5**	**SSS**	**96.4**	**177.6**	**–45.4**	**78.1**	**–34.0**
141	5.3	SSS	97.6	176.1	69.3	–63.3	–30.0
142	4.5	SSS	97.7	176.1	61.5	60.7	–30.0
143	4.8	SSS	97.7	176.1	62.1	180.0	–30.0
144	20.1	RSS	89.7	176.1	78.6	–61.7	37.9
145	20.0	RSS	89.7	176.4	111.3	73.8	38.2
146	20.3	RSS	89.7	176.4	74.6	179.6	38.2
147	11.9	SSS	135.9	–22.5	61.3	60.6	–30.3
148	16.0	RSS	152.0	–168.7	–162.2	–60.8	38.7
149	14.9	RSS	155.5	–172.0	–163.2	61.7	38.6
150	16.3	RSS	152.7	–166.2	–163.1	179.3	38.9
151	17.7	RSS	152.8	–168.4	78.5	–61.7	39.0
152	17.5	RSS	152.8	–168.5	73.9	61.6	39.3
153	17.8	RSS	152.8	–168.5	74.7	179.5	39.3
154	1.1	SSS	150.7	169.9	–176.3	–62.3	–30.6
155	0.0	SSS	150.8	169.8	–174.2	61.3	–30.6
156	1.0	SSS	150.7	169.9	–176.7	180.0	–30.6
157	27.3	SSS	166.0	171.4	–163.9	–61.2	39.6
158	26.3	SSS	165.9	171.5	–165.0	61.1	39.5
159	27.3	SSS	165.9	171.5	–164.2	179.5	39.5
160	16.9	SSS	151.4	169.2	–45.7	78.2	–34.6
161	13.6	SSS	151.3	169.4	–52.1	180.0	–34.5
162	1.6	SSS	150.7	169.8	69.3	–63.3	–30.5
163	0.8	SSS	150.7	169.9	61.5	60.7	–30.5
164	1.2	SSS	150.7	169.9	62.1	180.0	–30.5
165	27.7	SSS	166.0	171.1	79.1	–61.5	39.4
166	27.4	SSS	166.4	171.1	73.9	61.4	39.8
167	27.9	SSS	166.3	171.5	74.9	179.5	39.8
168	*21.1*	*RSS*	*–145.7*	*42.1*	*60.2*	*–179.9*	*–31.7*

[a] See footnote *a* to Table V.
[b] See footnote *b* to Table V.