

Application of Cluster Analysis in Search of Low-energy Conformations by the Overlapping Spheres Method*

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RECEIVED DECEMBER 20, 2002; REVISED MARCH 5, 2003; ACCEPTED MARCH 10, 2003

Key words
cluster analysis
Ward's method
conformational analysis
global optimization
amino acids
copper(II) complexes

In order to achieve a general procedure for molecular fragmentation in the overlapping spheres (OS) method, aimed to search for low-energy conformations, cluster analysis (Ward's method) was applied. The center of the central sphere was situated at the geometrical center of the larger of two clusters, *i.e.*, molecular fragments. The new procedure was tested on three aliphatic hydrocarbon molecules with various degrees of branching, and on three diastereoisomers of copper(II) bis-chelates with 1-[*N*-(*tert*-butoxycarbonyl)amino]-2-hydroxymethylcyclopropane-1-carboxylic acid. The newly proposed procedure is more efficient than the old one (based on topological fragmentation) and is suitable for automation. However, Ward's method offers little or no advantage for molecules possessing some kind of symmetry, yielding virtually identical fragments.

INTRODUCTION

The overlapping spheres (OS) approach encompasses a variety of methods, all of which have in common the calculation of the overlapping volume of van der Waals spheres of constituent atoms, or any spheres defined in a systematic way. This term is a novel one: it independently appeared as the name for the method aimed at constructing a molecular geometric structure from the constitutional formula (*i.e.*, molecular topology),^{1–3} and for the method developed for finding low-energy conformations.⁴ But, putting aside the question of terminology, the roots of the OS method can be traced as far back as 1970, when the first Hopfinger and Scheraga's papers on the hydration shell model aimed at calculating the Gibbs energy of solvation appeared.^{5,6} This model was later used in molecular modeling⁷ and for the study of solva-

tion influence on the diastereoselectivity effects in coordination compounds.⁸ Also, a sort of overlapping spheres algorithm can be found in methods for molecular modeling of ligand-receptor interactions (docking), such as Kuntz's algorithm,⁹ or in procedures that explicitly use excluded volumes in drug design.¹⁰

Finding the conformation with the lowest energy (*i.e.*, global minimum of the conformational potential) is undoubtedly the central problem in conformational analysis of our days. Many approaches and methods were developed in order to find the most stable conformation without the need to check all the possible conformations of a compound:^{11–13} molecular dynamics,^{14,15} Monte Carlo,^{16,17} simulated annealing,¹⁸ low-mode search method,¹⁹ genetic algorithms,²⁰ and many others. The problem associated with all these methods is that there is not and there cannot be a general solution to the problem; in spite of the sophistica-

* Dedicated to Professor Nenad Trinajstić on the occasion of his 65th birthday.

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tion and high efficiency of the above-mentioned methods, it is impossible to obtain the global minimum of the conformational potential analytically, in an exact way. Therefore, there is a need for development of new methods aimed at this goal.

The overlapping spheres method for finding low-energy conformations^{4,21–24} is based on the construction of the central sphere (defined by its radius, R_v), centered at the geometrical center of the molecule or molecular fragment. A repulsive potential is proposed, which acts on the atoms penetrating the sphere, changing in this way the molecular conformation (see Methods). Such a simple model, requiring only two parameters to be defined – radius and position of the central sphere – has also its shortcomings. There is no *a priori* criterion for proper molecular fragmentation and the choice of the central sphere radius. In an analysis of fragmentation,²³ it was found that the best results were obtained if the center of the central sphere was situated at the geometrical center of the molecular fragment with the maximal degree of symmetry and possessing an aliphatic chain, as long as possible. This finding was further confirmed in the case of structurally quite complex molecules of copper(II) mono- and bis-chelates with 1-[*N*-(*tert*-butoxycarbonyl)amino]-2-hydroxymethylcyclopropane-1-carboxylic acid (*N*-Boc-ACC-OH).²⁴

The first aim of our work is to find a general procedure for fragmentation of molecules by applying cluster analysis (Ward's method) to the molecules studied. In contrast to the previously used topological fragmentation, the new approach has the advantage of its strong dependence on the initial molecular conformation. This means that the direction of the conformational search is dependent on the overall molecular structure (topography), not only on molecular topology. The second aim of our research is to find the best general strategy for the search for low-energy conformations. We have therefore checked two approaches: the first selects the conformation with the lowest energy after each step (sieve method),^{21,23} and the second follows the protocol irrespectively of the results obtained (stream method).²⁴ The former problem is discussed in the second part of the Results and Discussion section, and the latter in its first paragraph.

METHODS

The overlapping spheres (OS) approach is based on the evaluation of the function:⁶

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

where V^* is the overlapping volume of the central sphere S_v (with radius R_v) and V_j volumes of van der Waals spheres s_j of the neighboring atoms. The central sphere is positioned at the geometrical center of the molecular fragment defined by the positions of the respective atoms.

In all calculations, only one V^* function was evaluated per molecule.

Total energy of the molecule is defined as:

$$V_{os} = kV^* + V_b + V_\theta + V_\chi + V_\varphi \quad (2)$$

where V_b , V_θ and V_χ are bonding, bond angle bending and out-of-plane potential, respectively, while 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 true for the torsional potential V_φ (the fifth term in Eq. 2), which was used only in the case of copper(II) complexes with *N*-Boc-ACC-OH. This potential was defined only for two torsional angles per chelate ring; its purpose is to prevent the change of ab-

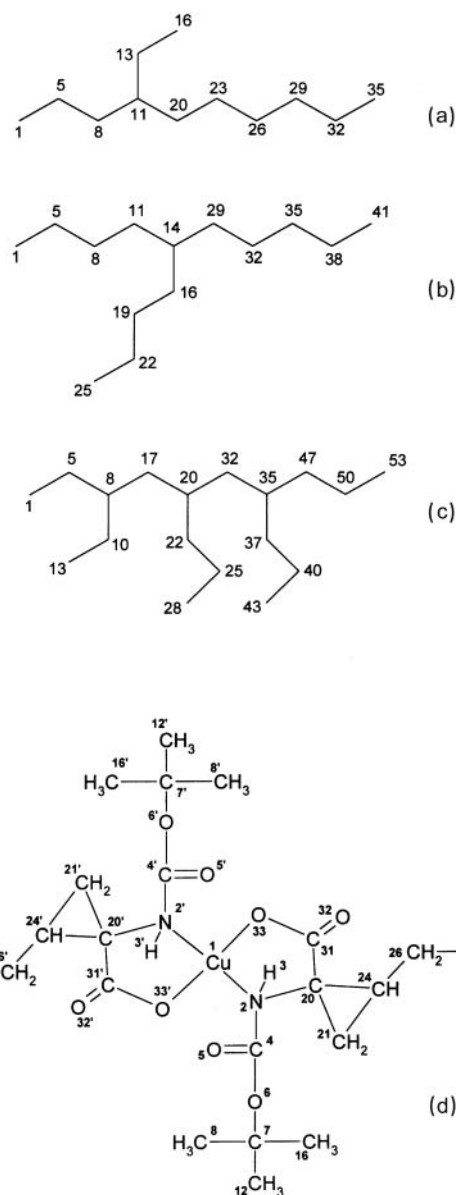


Figure 1. Molecules checked in the OS procedure with the respective numbering schemes: (a) 4-ethyldecane, (b) 5-butyldecane, (c) 3-ethyl-5,7-dipropyldecane and (d) *trans*-(*N*-Boc-ACC-OH)₂Cu.

solute configuration of atoms C(20), C^α, and C(24), C^β (Figure 1) during the course of minimization.²⁴ Parameter k (Eq. 2) was taken to have an arbitrary value 21 MJ mol⁻¹ nm⁻³, whereas the rest of the 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 ($k_{N-M-O} = k_{N-M-X} = k_{O-M-X} = 97.784$; *c.f.* force field FF1).^{25,26}

After 1000 steepest-descent iterations on the initial («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). A heavily distorted structure was usually obtained, which was further subjected to a regular molecular-mechanics procedure (Figure 2). The full description of the model, as well as its parameterization is given elsewhere.²³

Molecular-mechanics Step

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

$$V_T = \frac{1}{2} \sum_i k_{b,i} (b_i - b_{0,i})^2 + \frac{1}{2} \sum_j k_\theta (\theta_j - \theta_{0,j})^2 + \frac{1}{2} \sum_k V_{n,k} (1 \pm \cos n_k \varphi_k) + \sum_l [A_l \exp(-Br_l) - C_l r_l^{-6}] + \frac{1}{2} \sum_m k_\chi \chi_m^2 \quad (3)$$

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_0 and θ_0 are 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 a Buckingham function with parameters A , B , and C . In addition, the out-of-plane deformation potential ($k_\chi = 100$ kcal mol⁻¹ rad⁻², 1 cal = 4.184 J) for the angle defining with four atoms (O–CO–N(C) groups) was also calculated. Other parameters for molecular-mechanics calculations are presented elsewhere.^{25,26}

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

Cluster Analysis

Ward's algorithm for cluster analysis joins a point to the cluster that has the minimal Euclidean distance between its geometrical center and the respective point.³⁰ The method uses the analysis of variance approach to evaluate the distance between clusters. It attempts to minimize the sum of squares of any two clusters that can be formed in each step.

The Cartesian coordinates of atoms constituting the molecule were taken as the initial set of points. Frag-

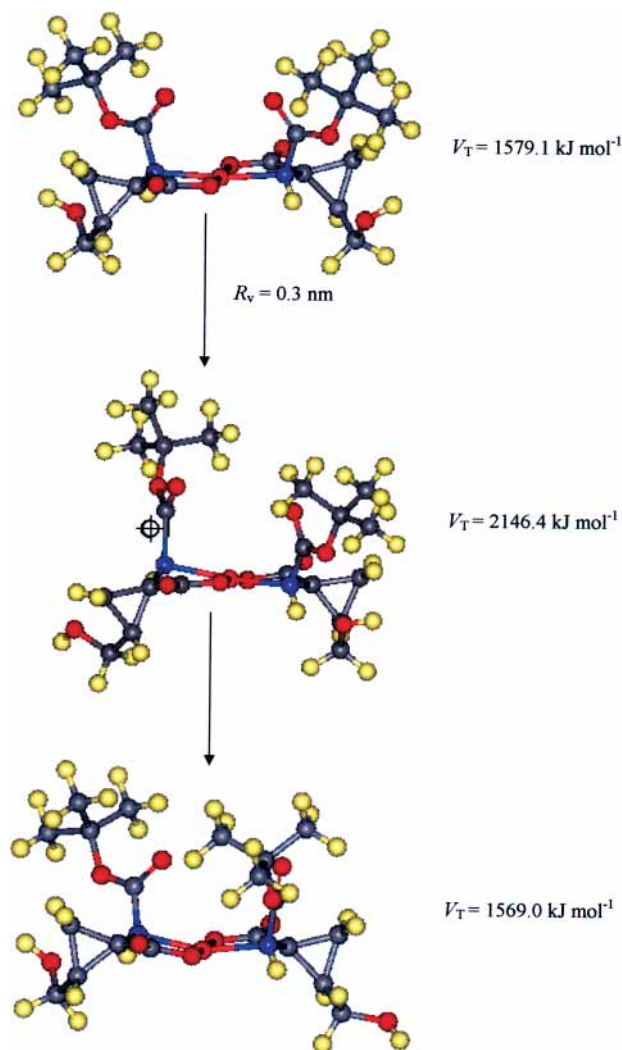


Figure 2. Application of the overlapping spheres method to the molecule of (SSR)(SSR) isomer of *trans*-(N-Boc-ACC-OH)₂Cu. After 1000 steepest descent interactions, a heavily distorted structure was obtained with the conformational energy 567.3 kJ mol⁻¹ above the initial, «seed» conformation. Starting from this structure, geometrical optimization by the regular molecular mechanical method yielded conformation with the energy 10.1 kJ mol⁻¹ below the energy of the «seed» conformation. The center of the central sphere ($R_v = 0.3$ nm) was situated at the geometrical center of the left chelate ring (its position is marked by a cross).

mentation of the molecule was obtained by splitting the whole molecule into two clusters. The cluster with more atoms was taken as the main fragment, *i.e.*, the fragment defining the center of the central sphere.

The cluster analysis was performed with the STATISTICA 5.5 program package.

RESULTS AND DISCUSSION

Comparison of the Two Search Strategies

As mentioned in the Introduction, the overlapping spheres method can be systematically used in two ways: by tak-

TABLE I. Comparison of the results obtained by the sieve and stream versions of the OS method on *trans*-(N-Boc-ACC-OH)₂Cu by using topological fragmentation

Configuration	Seed conformation		Fragmentation ^(b)	Number of runs	Number of obtained conformations	V_{\min} / kJ mol ⁻¹	Number of conformations with $V < V_{\text{seed}}$	Number of conformations with $V > V_{\text{seed}}$			
	Conformational energy, ^(a) V_{seed} / kJ mol ⁻¹										
(SSR)(SSR)	25.5		r1,r2,...r6	24	11	0.0	11	0			
									s1,s2,...s6	17	0
									t1,t2,...t9	5	0
(RSR)(SRS)	35.3		r1,r2,...r6	24	13	6.0	13	0			
									s1,s2,...s6	7	1
									t1,t2,...t9	3	0
(RSS)(SRR)	29.3		r1,r2,...r6	24	17	6.0	15	2			
									s1,s2,...s6	11	0
									t1,t2,...t9	3	0
<i>Stream method</i>											
(SSR)(SSR)	25.5		r1,r2,...r6	24	16	0.4	16	0			
									s1,s2,...s6	10	0
									t1,t2,...t9	7	0
(RSR)(SRS)	35.3		r1,r2,...r6	24	13	5.7	13	0			
									s1,s2,...s6	10	0
									t1,t2,...t9	14	0
(RSS)(SRR)	29.3		r1,r2,...r6	24	7	4.0	6	1			
									s1,s2,...s6	9	0
									t1,t2,...t9	9	0
<i>Sieve method</i>											
(SSR)(SSR)	25.5		r1,r2,...r6	24	16	0.4	16	0			
									s1,s2,...s6	10	0
									t1,t2,...t9	7	0
(RSR)(SRS)	35.3		r1,r2,...r6	24	13	5.7	13	0			
									s1,s2,...s6	10	0
									t1,t2,...t9	14	0
(RSS)(SRR)	29.3		r1,r2,...r6	24	7	4.0	6	1			
									s1,s2,...s6	9	0
									t1,t2,...t9	9	0

^(a) All energy values are given relative to the lowest-energy conformation ($V_T = 1553.6$ kJ mol⁻¹). For details see Supplement, Table VI, and Ref. 24.

^(b) Fragmentation scheme: C(8,12,16)H₃O(6)-C(4)O-N(2)H-C(20)-C(21)H₂-C(24)H-C(26)H₂-O(29)H (r1-r3; r4-r6 is the same, but defined by the other chelate ring), C(8',12',16')H₃-O(6')-C(4')O-N(2')H-Cu(1)-O-C(31)O-C(20)-C(24)H-C(26)H₂-O(29)H (s1-s3; s4-s6 is the same, but starting from the other chelate ring), C(8,12,16)H₃-O(6)-C(4)O-N(2)H-Cu(1)-N(2')H-C(4')O-O(6')-C(8',12',16')H₃ (t1-t3); C(8)---C(8',12',16'), t2-t6: C(12)---C(8',12',16'), t7-t9: C(16)---C(8',12',16'). For the atom numbering scheme see Figure 1.

ing, after each step, the conformation with the lowest energy (sieve method), or by following the procedure irrespectively of the obtained results (stream method). To compare these two strategies, we checked the three diastereomers of copper(II) bis-chelate with *N*-Boc-ACC-OH (Table I, Figure 1).

In both approaches the central sphere radius (R_v) was changed from 0.3 to 0.6 nm, in 0.1 nm steps. In the sieve method, all the proposed topological fragments (r1–r6, s1–s6 or t1–t9) were applied in each step. Among all the obtained conformations, the one with the lowest energy was chosen as the »seed« conformation for the next OS computation step. In the case of the stream method, the fragmentation was changed in each step, simultaneously with the rise of the central sphere radius.

Starting from the same »seed« conformations, the stream method yielded 87 conformations in 171 minimization runs, and the sieve method gave 95 conformations after 252 runs. This gives the efficiency of 51 % and 38 % for the stream and sieve method, respectively (Table I). The lowest-energy conformation was usually obtained more rapidly by the stream method, although in some cases (3 out of 9 pairs) the conformation with the lowest energy was obtained by the sieve method. All this shows that the stream method is better fitted for the search for low-energy conformations. This conclusion is also confirmed by the results discussed in the next paragraph.

Topographical Fragmentation: Fragments Obtained Using the Cluster Analysis

For systematic comparison of the method of topological *vs.* topographical fragmentation we chose three branched hydrocarbons extensively studied previously:^{21,23} (*S*)-4-ethyldecane, 5-butyldecane, and heavily branched 3-ethyl-5,7-dipropyldecane (Figure 1). Besides these hydrocarbons, the three isomers – the same as in the previous paragraph – of copper(II) bis-chelate with *N*-Boc-ACC-OH were also subjected to the OS procedure.

In contrast to the results presented in Table I, Table II does not analyze conformations obtained after the lowest-energy conformation was reached. As can be seen in Figure 3 and from the results presented in the Supplement, it does not make much sense to use the OS method after the drop of energy in the first few steps, except as a vehicle for the generation of conformations irrespectively of their energy. The conformations with the lowest energy were obtained unexpectedly fast, after 1 to 4 steps, by all studied methods (topological and topographical fragmentation, sieve and stream method alike). The final result was mostly dependent on the initial, »seed« conformation, but not less on the fragmentation

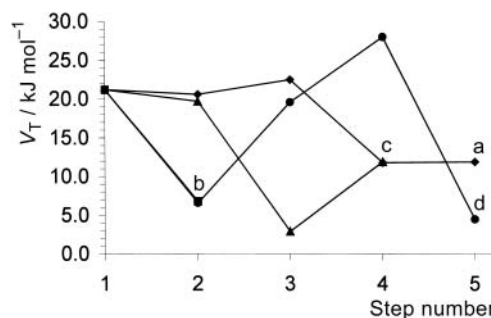


Figure 3. The OS runs for 4-ethyldecane starting from the same »seed« conformation ($g\ g\ (t)g\ g\ g\ t\ g$, $V_T = 21.2\ \text{kJ mol}^{-1}$). Runs a, b, and c were obtained by topological, and run d by topographical fragmentation. For details see Supplement, Tables I and VII.

and the central sphere radius. The same »seed« conformation of 4-ethyldecane ($V_T = 21.2\ \text{kJ mol}^{-1}$) yielded the lowest-energy conformation, $V_T = 11.8\ \text{kJ mol}^{-1}$, in three steps, but following the other protocol it gave the conformation $V_T = 6.8\ \text{kJ mol}^{-1}$ in only one step, and following the third protocol the conformation $V_T = 2.9\ \text{kJ mol}^{-1}$ was obtained after two steps.

Comparing the data presented in Table II, it is evident that the fragments obtained using the cluster analysis generally give the best results in terms of all three criteria: the mean number of steps per run, the lowest energy obtained, and the mean drop of energy per step. The best improvement was obtained for 5-butyldecane. In all four runs, the conformation with the lowest energy was obtained after only one step. Moreover, in spite of slightly higher energy of the conformation obtained by topographical fragmentation (2.5 *vs.* 1.5 kJ mol^{-1}), it has to be borne in mind that the latter conformation was obtained after 16 runs. The advantage of the topographical fragmentation is even more evident in the case of the heavily branched molecule of 3-ethyl-5,7-dipropyldecane (Figure 4). Because only two topological fragments (1–9 & 17–56, 1–21 & 32–56)* were found suitable for the OS procedure,²³ the maximal number of conformations obtained from a »seed« conformation did not exceed four. In contrast, it was possible to obtain up to 12 conformations from a »seed« conformation by applying the topographical fragmentation (Supplement, Table IX). The large number of conformations obtained is evidently due to several (11) topographical fragments that appeared after the application of Ward's method (1–31, 1–34, 1–36, 17–36, 17–56, 20–56, 22–56, 25–56, 1–19 & 35–56, 1–36 & 47–49, 17–21 & 32–56).

Fragmentation by the cluster analysis did not prove so successful in the case of 4-ethyldecane and copper(II) diastereomeric bis-chelates with *N*-Boc-ACC-OH, except

* Fragments are defined by constituent atoms according to the numbering scheme in Figure 1.

TABLE II. General comparison of the OS method

	Sieve method, topological fragmentation ^(a)	Stream method, topological fragmentation	Topographical fragmentation (cluster analysis) ^(b)
4-ethyldecane			
Number of runs	5	11	5
Mean number of steps per run	3.0	2.1	3.2
Energy of the lowest conformation / kJ mol ⁻¹	2.1	2.9	2.5
Mean drop of energy per step / kJ mol ⁻¹	-5.9	-6.1	-4.8
5-butyldecane			
Number of runs	3	16	4
Mean number of steps per run	2.7	2.3	1.0
Energy of the lowest conformation / kJ mol ⁻¹	2.8	1.5	2.5
Mean drop of energy per step / kJ mol ⁻¹	-8.0	-8.9	-17.7
3-ethyl-5,7-dipropyldecane			
Number of runs	5	4	3
Mean number of steps per run	1.8	1.5	2.0
Energy of the lowest conformation / kJ mol ⁻¹	25.5	25.5	19.5
Mean drop of energy per step / kJ mol ⁻¹	-6.0	-9.3	-9.2
<i>trans</i> -(<i>N</i> -Boc-ACC-OH) ₂ Cu			
Number of runs	9	9	3 (3)
Mean number of steps per run	3.3	6.8	2.7 (3.3)
Energy of the lowest conformation / kJ mol ⁻¹ ^(c)	0.4, 4.0, 5.7	0.0, 6.0, 6.0	0.6, 29.0, 17.8 (2.0, 3.1, 17.8)
Mean drop of energy per step / kJ mol ⁻¹	-6.9	-3.1	-5.3 (-6.7)

^(a) Taken from Ref. 23.

^(b) Applied as the stream method; data obtained by the sieve variant are given in the parentheses.

^(c) The first, second, and third values correspond to (*SSR*)(*SSR*), (*RSS*)(*SRR*), and (*RSR*)(*SRS*) isomers, respectively. Zero value: 1553.6 kJ mol⁻¹.

for (*SSR*)(*SSR*). The cluster analysis in this case showed little advantage over the method of topological fragmentation, if any. This finding should be attributed to the symmetry of the molecules, which leads to uniformity of the fragments obtained by cluster analysis. 4-Ethyldecane yielded six topographical fragments (1–19, 1–22, 1–25, 1–28, 11–38, 20–38), but usually the molecule had been split into two clusters (1–19 and 20–38) with the same number of atoms. Moreover, these clusters correspond to the most widely used topological fragments. The same holds true for copper(II) bis-complexes of *N*-Boc-ACC-OH, which upon cluster analysis, in all cases but one, yielded two clusters corresponding to chelate rings (Figure 2). It is noteworthy that better results were obtained for the complex possessing a *C*₂ element of symmetry, (*SSR*)(*SSR*), than for the complexes with a center of symmetry, (*RSS*)(*SRR*) and (*RSR*)(*SRS*). Starting from the same »seed« conformation

by using the topographical fragmentation, a conformation was obtained with virtually the same energy as in topological fragmentation for the (*SSR*)(*SSR*) isomer. However, conformations of considerably higher energies were obtained for isomers (*RSS*)(*SRR*) and (*RSR*)(*SRS*), especially for the latter one (Table II).

CONCLUSIONS

The application of cluster analysis in order to obtain fragments better suited for the search for low-energy conformations by using the overlapping spheres method shows that the new method is generally more efficient than the old one, based on topological fragmentation. Besides, the new way of fragmentation enables automatic application of the OS method, because the molecular fragments and, accordingly, the position of the cen-

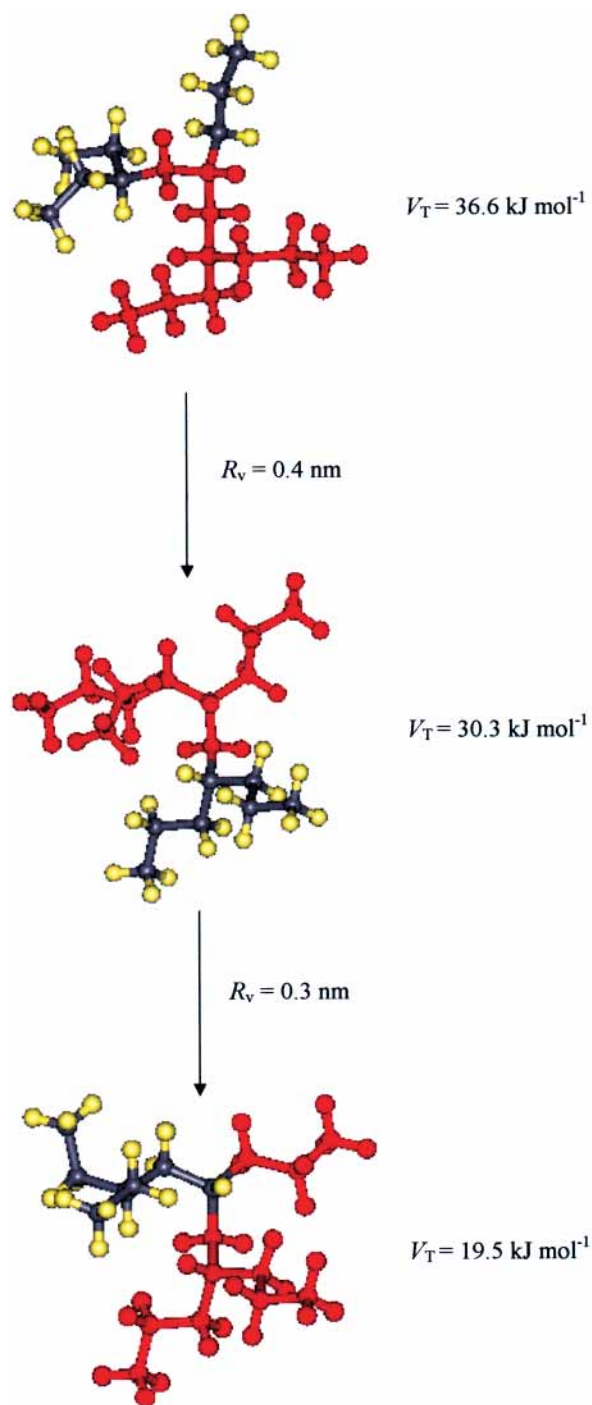


Figure 4. Application of the topographical version of the OS method to 3-ethyl-5,7-dipropyldodecane (Supplement, Table IX). The main molecular fragment is marked red.

tral sphere, is not directed by loose rules or, worse, by the intuition of the scientist, but by a strict mathematical algorithm. In spite of this, topological fragmentation gives sometimes better results, especially in the case of symmetric molecules. Hence, we strongly encourage application of both methods in the search for the low-energy conformations.

Supplementary Materials. – Due to the large volume of data, Tables III–IX are prepared as the Supplement. This material may be found on WWW under <http://pubwww.srce.hr/ccacaa> and is available on request from authors.

Acknowledgements. – We thank Diana Šimić, Ph.D., head of the Biomathematics Unit of our Institute, for her help with cluster analysis.

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SAŽETAK

Primjena klasterne analize za pronalaženje konformacija niskih energija metodom preklapanja kugli

Nenad Raos i Lora Žuža-Mak

U namjeri da se izvede opća metoda fragmentacije molekule za metodu preklapanja kugli (*overlapping spheres*, OS) – koja je namijenjena pronalaženju konformacija niskih energija – primijenjena je Wardova metoda klasterne analize. Centar središnje kugle postavljen je u geometrijsko središte većeg klastera (molekularnoga fragmenta). Novi je postupak iskušan na tri molekule alifatskih ugljikovodika različitoga stupnja grananja i na tri diastereomera bakrovog(II) bis-kelata 1-[*N*-(*tert*-butoksikarbonil)amino]-2-hidroksimetilciklopropan-1-karboksilne kiseline. Novi je postupak djelotvorniji od staroga (koji se temeljio na topološkoj fragmentaciji), a pogodan je i za automatizaciju. Wardova metoda, međutim, gotovo da nema prednosti kada se primjenjuje na molekule koje su bar donekle simetrične, budući da generira gotovo identične fragmente (klustere).

Application of Cluster Analysis in Search of Low-energy Conformations by the Overlapping Spheres Method

Nenad Raos and Lora Žuža-Mak

SUPPLEMENT

TABLE III. Application of the topological fragmentation method for OS calculations on (S) 4-ethyldecane

Step	R_v nm	Main fragment ^(a)	V_T kJ mol ⁻¹	Conformation
0	–	–	21.2	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg
1	0.3	1–12, 20–38	20.6	g ⁻ g ⁻ (t)g ⁻ tg ⁻ tg
2	0.4	1–12, 20–38	22.5	g ⁻ g ⁻ (g)ttttg ⁻
3	0.5	1–12, 20–38	11.8	tt(g)g⁻tttt
4	0.6	1–12, 20–38	11.9	tt(g)tttt
0	–	–	21.2	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg
1	0.3	20–38	19.7	g⁻g⁻(t)g⁻g⁻g⁻tt
2	0.4	20–38	21.7	g ⁻ g ⁻ (t)tttt
3	0.6	20–38	20.2	g ⁻ g ⁻ (g)tttt
0	–	–	21.2	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg
1	0.3	1–10	6.8	tg⁻(g)g⁻g⁻g⁻tg⁻
0	–	–	21.2	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg
1	0.5	13–19	19.7	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg ⁻
2	0.6	13–19	19.6	g⁻t(g)g⁻tg⁻tg
0	–	–	21.2	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg
1	0.6	13–19	19.7	tg ⁻ (g)g ⁻ g ⁻ g ⁻ gg
2	0.6	20–38	2.9	tg⁻(t)g⁻tttt
3	0.6	1–12, 20–38	11.9	tt(g)tttt
0	–	–	21.2	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg
1	0.6	1–12, 20–38	8.6	tg ⁻ (t)g ⁻ g ⁻ g ⁻ g ⁻
2	0.6	20–38	16.5	tg ⁻ (t)g ⁻ tttt
3	0.6	1–10	13.6	tg ⁻ (t)ttggt
4	0.6	13–19	5.8	tg⁻(g)ttggt
0	–	–	19.8	tg ⁻ (t)g ⁻ g ⁻ gtg
1	0.6	13–19	6.9	tt(t)g ⁻ tttg
0	–	–	19.8	tg ⁻ (t)g ⁻ g ⁻ gtg
1	0.3	20–38	6.0	tg ⁻ (t)g ⁻ tggt
2	0.4	20–38	11.6	tg ⁻ (t)tttt
3	0.6	20–38	2.9	tg⁻(t)g⁻tttt
0	–	–	19.8	tg ⁻ (t)g ⁻ g ⁻ gtg
1	0.3	1–12, 20–38	6.3	tg ⁻ (t)g ⁻ ttgg
2	0.4	1–12, 20–38	5.5	tg⁻(g)ttttg
3	0.6	1–12, 20–38	11.9	tt(g)tttt
0	–	–	19.8	tg ⁻ (t)g ⁻ g ⁻ gtg
1	0.6	1–12, 20–38	11.9	tt(t)tttt
2	0.6	20–38	4.5	tt(t)g⁻tttt
0	–	–	19.8	tg ⁻ (t)g ⁻ g ⁻ gtg
1	0.6	13–19	6.9	tt(t)g ⁻ tttg
2	0.6	20–38	4.5	tt(t)g⁻tttt
3	0.6	1–12, 20–38	11.9	tt(t)tttt

^(a) According to the atom numbering scheme in Figure 1.

TABLE IV. Application of the topological fragmentation method for OS calculations on 5-butyldecane

Step	R_v nm	Main fragment ^(a)	V_T kJ mol ⁻¹	Conformation	(cont.)				
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	3	0.6	14, 15, 29–44	9.2	$g^{tt}(ttg^-)g^-tg^-t$
1	0.4	1–15, 29–44	8.5	$ttg^-(gtg^-)tttt$	4	0.6	14–44	5.3	$ttt(ttt)g^-ttt$
2	0.5	1–15, 29–44	13.8	$g^-tt(gtg^-)g^-ttt$	5	0.6	1–28	9.2	$ttg(ttt)g^-ttt$
3	0.6	1–15, 29–44	9.3	$ttt(gt)g^- ttt$	6	0.6	1–15, 29–44	9.0	$ttt(ttt)tttt$
4	0.4	1–15, 29–44	12.6	$g^{tt}(gt)g^-ttt$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
5	0.5	1–15, 29–44	15.0	$g^{tt}(gtg^-)tttt$	1	0.6	1–15, 29–44	9.3	$ttt(gt)g^-ttt$
6	0.6	1–15, 29–44	9.4	$ttt(gt)tttt$	2	0.6	1–15	16.8	$ttt(tt)g^-g^{tt}$
7	0.3	1–15, 29–44	15.2	$ttt(ggt)ttg^-t$	3	0.6	1–15, 29–44	9.3	$ttt(gt)g^-ttt$
8	0.4	1–15, 29–44	17.1	$g^{tt}(ggt)g^-ttg$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
9	0.5	1–15, 29–44	12.7	$ttt(gtg^-)tttt$	1	0.6	1–25	19.4	$ttg^-(g^-tg^-)g^-g^-g^-t$
10	0.6	1–15, 29–44	9.2	$ttt(gt)tttt$	2	0.6	14–28	16.3	$gtg(gt)g^-g^-g^-t$
11	0.3	1–15, 29–44	15.0	$ttg(ggg^-)g^-ttg$	3	0.6	14, 15, 29–44	16.5	$gtg(gtg^-)g^-tg^-t$
12	0.4	1–15, 29–44	22.6	$g^{tt}(ggg^-)g^-ttg$	4	0.6	14–44	8.9	$ttg(gt)g^{ttt}$
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	5	0.6	1–15, 29–44	9.3	$ttt(gt)g^-ttt$
1	0.4	14, 15, 29–44	25.5	$g^-tg^-(g^-g^-g^-)g^-ttt$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
2	0.6	14, 15, 29–44	17.9	$g^-tt(g^-g^-g^-)g^-ttt$	1	0.3	1–15, 29–44	43.7	$ttg^-(g^-g^-g^-)g^{tt}g^-$
3	0.5	14, 15, 29–44	16.1	$g^-tt(g^-g^-g^-)g^-ttt$	2	0.4	1–15, 29–44	28.6	$g^-tt(g^-g^-g^-)g^{tt}g^-$
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	3	0.5	1–15, 29–44	14.7	$g^-tt(gtg^-)tttt$
1	0.3	1–15	4.3	$ttg^-(ggt)g^-g^-g^-t$	4	0.6	1–15, 29–44	9.4	$ttt(gt)tttt$
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
1	0.3	14–18	25.8	$g^-g^-g^-(ggt)g^-g^-g^-t$	1	0.3	1–28	5.0	$gtg^-(g^{tt})g^-g^-g^-t$
2	0.6	14–18	17.4	$g^-tg^-(g^{tt})g^-g^-g^-t$	2	0.4	1–28	17.9	$gtg(tt)g^-g^-g^-t$
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	3	0.5	1–28	14.9	$ttg^-(g^{tt})g^-g^-g^-g$
1	0.3	1–28	17.4	$g^-tg^-(g^{tt})g^-g^-g^-t$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
2	0.4	1–28	15.6	$g^-tg^-(ttt)g^-g^-g^-t$	1	0.3	14–44	28.4	$ttg^-(g^-g^-g^-)g^-tg^-t$
3	0.5	1–28	25.1	$ttt(tgt)g^-tg^-g$	2	0.4	14–44	5.1	$ttg^-(gtg^-)g^-tg^-t$
4	0.6	1–28	11.8	$ttg^-(ttt)g^-ttg$	3	0.5	14–44	4.4	$g^-tt(ttt)g^-ttt$
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
1	0.5	16–44	5.3	$g^-g^-t(g^-tg^-)g^-ttt$	1	0.5	1–15	16.1	$ttg^-(gtg^-)g^-g^-gt$
2	0.6	16–44	1.5	$g^-tt(ttt)g^-ttt$	2	0.6	1–15	7.1	$ttg^-(ttg)g^-tgt$
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
1	0.6	1–15, 29–44	16.2	$tg^-g^-(ttg^-)g^-g^-tt$	1	0.3	14–28	15.8	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
2	0.6	14–44	9.3	$ttt(gt)g^-ttt$	0	–	–	32.7	$ttg^-(g^-g^-g^-)g^-g^-g^-t$
3	0.6	1–15	16.8	$ttt(tt)g^-g^{tt}$	1	0.3	14, 15, 29–44	25.4	$ttg(g^-g^-g^-)g^-g^-tt$
0	–	–	25.3	$g^-g^-g^-(tg^-g^-)g^-g^-g^-t$	2	0.4	14, 15, 29–44	23.2	$ttg(g^-g^-g^-)g^-ttt$
1	0.6	1–15	18.2	$ttt(ttg^-)g^-g^-g^-g$	3	0.6	14, 15, 29–44	5.3	$ttg(g^-tg^-)tttt$
2	0.6	14–28	5.8	$ttt(ttg^-) g^-g^-g^-t$					

(a) According to the atom numbering scheme in Figure 1.

TABLE V. Application of the topological fragmentation method for OS calculations on 3-ethyl-5,7-dipropyldecane

Step	R_V nm	Main fragment ^(a)	V_T kJ mol ⁻¹	Conformation
0	–	–	43.3	t(g ⁻)gt(gg ⁻)g ⁻ t(g ⁻ g ⁻)tt
1	0.6	1–9, 17–56	29.6	t(g⁻)gg(g⁻t)tg⁻(g⁻g⁻)tt
2	0.6	1–21, 32–56	30.1	t(g ⁻)gg(gt)tg ⁻ (g ⁻ t)tt
3	0.6	1–9, 17–56	38.0	t(g ⁻)gg(gt)tg ⁻ (tt)tt
4	0.6	1–21, 32–56	40.7	g ⁻ (g ⁻)g ⁻ g(gt)tg ⁻ (tt)tt
5	0.6	1–9, 17–56	39.3	g ⁻ (g ⁻)g ⁻ g(gt)tg ⁻ (tt)tt
0	–	–	43.3	t(g ⁻)gt(gg ⁻)g ⁻ t(g ⁻ g ⁻)tt
1	0.6	1–21, 32–56	32.5	g ⁻ (g ⁻)gg(gt)tg ⁻ (gt)tt
2	0.6	1–9, 17–56	32.4	t(g ⁻)gg(gt)tg ⁻ (gt)tt
3	0.6	1–21, 32–56	25.5	g⁻(g⁻)g⁻g(gt)tt(gt)tt
0	–	–	43.3	t(g ⁻)gt(gg ⁻)g ⁻ t(g ⁻ g ⁻)tt
1	0.3	1–9, 17–56	29.6	t(g⁻)gg(gt)tg(g⁻g⁻)tt
2	0.4	1–9, 17–56	31.9	t(g ⁻)gg(gt)tg ⁻ (g ⁻ g ⁻)tt
3	0.5	1–9, 17–56	37.4	t(g ⁻)gg(gt)g ⁻ g ⁻ (tt)tt
4	0.6	1–9, 17–56	46.3	g ⁻ (g ⁻)g ⁻ t(gt)g ⁻ g ⁻ (tt)tt
0	–	–	43.3	t(g ⁻)gt(gg ⁻)g ⁻ t(g ⁻ g ⁻)tt
1	0.4	1–21, 32–56	32.5	t(g⁻)gg(gt)tg⁻(g⁻g⁻)tg⁻

(a) According to the atom numbering scheme in Figure 1.

TABLE VII. Application of Ward's cluster analysis for OS calculations on 4-ethyldecane

Step	R_V nm	Main fragment ^(a)	V_T kJ mol ⁻¹	Conformation
0	–	–	24.4	gt(g)tttg ⁻ g
1	0.4	1–19	24.1	tt(t)tttg ⁻ g
2	0.4	11–38	15.6	gg ⁻ (g)tttt
3	0.4	1–19	16.7	tg ⁻ (t)ttgtg ⁻
4	0.4	1–28	7.9	tg⁻(g)ttgtg⁻
5	0.4	1–22	16.7	tg ⁻ (t)ttgtg ⁻
0	–	–	21.2	g ⁻ g ⁻ (t)g ⁻ g ⁻ g ⁻ tg ⁻
1	0.4	1–19	6.6	tg ⁻ (t)g ⁻ g ⁻ g ⁻ tg ⁻
2	0.4	1–25	19.6	tt(t)g ⁻ tg ⁻ gg
3	0.4	1–22	28.0	tt(t)ttg ⁻ gg
4	0.4	20–38	4.5	tt(t)g⁻tttt
0	–	–	20.6	g ⁻ g ⁻ (t)g ⁻ tg ⁻ tg
1	0.4	1–19	7.4	tg ⁻ (t)g ⁻ tg ⁻ tg
2	0.4	20–38	2.9	tg⁻(t)g⁻tttt
3	0.3	1–28	4.5	tt(t)g ⁻ tttt
4	0.4	1–28	11.8	tt(g)g ⁻ tttt
0	–	–	19.8	tg ⁻ (t)g ⁻ g ⁻ gtg
1	0.4	20–38	11.6	tg ⁻ (t)tttt
2	0.4	1–28	2.6	tg ⁻ (g)g ⁻ tttt
3	0.4	1–19	2.5	tg⁻(t)g⁻tttt
4	0.4	1–28	4.5	tt(t)g ⁻ tttt
0	–	–	14.3	g ⁻ t(t)tttt
1	0.4	1–28	11.6	tg ⁻ (t)tttt
2	0.3	1–28	11.8	tt(g)g ⁻ tttt
3	0.4	1–19	6.2	tt(t)g⁻tttt

(a) According to the atom numbering scheme in Figure 1.

TABLE VI. Application of the topological fragmentation for OS calculations, in the sieve mode, on *trans*-bis-complexes of *N*-Boc-ACC-OH with copper(II)^(a)

Step	R_V nm	Fragment	V_T kJ mol ⁻¹	Conformation ^(b)
<i>(SSR)</i> / <i>(SSR)</i>				
0			1579.1	98–98
1	0.3	r2	1568.0	97–98
2	0.4	r4	1557.6	97–115
3	0.5	r3	1556.9	101–115
4	0.6	r5	1555.7	100–95
0			1579.1	98–98
1	0.3	s2	1554.3	41–97
2	0.6	s4	1555.8	102–95
0			1579.1	98–98
1	0.3	t1	1556.4	95–95
2	0.4	t3	1554.1	96–41
3	0.6	t9	1554.0	95–41
<i>(RSR)</i> / <i>(SRS)</i>				
0			1588.9	80–80
1	0.3	r4	1574.4	80–3
2	0.4	r1	1560.8	49–3
3	0.5	r2	1560.8	47–2
4	0.6	r3	1560.6	47–48
0			1588.9	80–80
1	0.3	s4	1584.1	110–109
2	0.4	s3	1562.2	82–78
3	0.5	s5	1561.7	2–22
4	0.6	s6	1561.3	3–22
0			1588.9	80–80
1	0.3	t2	1585.2	110–80
2	0.4	t7	1562.1	79–69
3	0.5	t1	1561.5	20–68
4	0.6	t7	1559.3	83–16
<i>(RSS)</i> / <i>(SRR)</i>				
0			1582.9	11–11
1	0.3	r1	1582.6	10–11
2	0.4	r4	1582.3	10–10
3	0.6	r1	1579.0	10–65
0			1582.9	11–11
1	0.3	s1	1570.0	151–7
2	0.4	s1	1567.2	153–102
3	0.5	s5	1562.5	7–8
4	0.6	s2	1562.9	8–8
0			1582.9	11–11
1	0.3	t6	1560.2	103–6
2	0.4	t2	1559.0	99–7
3	0.5	t7	1557.6	98–7
4	0.6	t2	1558.0	98–8

(a) Fragments r1–r6 (the same as 1–6, Table II, Ref. 24), s1–s6 (11–16, Table III, Ref. 24), and t1–t9 (1–9, Table IV, Ref. 24), see Table I.

(b) Denoted as in Ref. 24.

TABLE VIII. Application of Ward's cluster analysis for OS calculations on 5-butyldecane

Step	$\frac{R_v}{\text{nm}}$	Main fragment ^(a)	$\frac{V_T}{\text{kJ mol}^{-1}}$	Conformation
0	–	–	32.7	ttg ⁻ (g ⁻ g ⁻ g ⁻)g ⁻ g ⁻ g ⁻ t
1	0.5	1–31	3.0	ttg⁻(gg⁻t)g⁻g⁻g⁻t
0	–	–	25.3	g ⁻ g ⁻ g ⁻ (tg ⁻ g ⁻)g ⁻ g ⁻ g ⁻ t
1	0.5	11–44	2.5	g⁻tg⁻(g⁻tt)g⁻t
2	0.5	1–28	9.2	ttg(gt)g ⁻ t
3	0.5	1–15, 29–44	2.7	ttg(gt)ttt
4	0.4	1–31	17.2	g ⁻ tg ⁻ (tt)g ⁻ tg ⁻ t
5	0.5	1–28	11.2	ttg(ttt)ttg
6	0.5	19–44	13.9	g ⁻ tt(gt)g ⁻ t
7	0.5	1–31	11.7	ttg(ttt)g ⁻ tg ⁻ t
8	0.5	1–15, 29–44	6.0	ttg(gt)g ⁻ ttt
9	0.5	1–28	9.9	ttg(ttt)ttt
10	0.5	14–44	6.0	gtg(ttt)g ⁻ t
11	0.5	1–28	9.9	ttg(ttt)g ⁻ t
12	0.5	1–15, 29–44	5.9	ttg(gt)g ⁻ ttt
0	–	–	16.8	ttt(tt)g ⁻ gt
1	0.5	1–34	5.1	ttt(tt)g⁻ttg
2	0.5	1–28	11.7	ttg(ttt)g ⁻ ttg
3	0.5	1–15, 29–44	5.9	ttg(gt)g ⁻ ttt
4	0.5	1–28	9.9	ttg(ttt)ttt
5	0.5	14–44	6.1	g ⁻ tt(ttt)g ⁻ t
6	0.5	1–28	9.9	ttg(ttt)g ⁻ t
7	0.5	1–15, 29–44	5.9	ttg(gt)g ⁻ ttt
8	0.5	1–28	9.9	ttg(ttt)ttt
0	–	–	9.3	ttt(gt)g ⁻ t
1	0.5	1–10, 16–28	2.8	ttg⁻(ttt)g⁻t
2	0.5	1–28	15.5	g ⁻ tg ⁻ (tt)g ⁻ t
3	0.5	1–15, 29–44	9.9	ttg(ttt)g ⁻ t
4	0.5	1–15, 29–44	6.0	ttg(gt)g ⁻ ttt
5	0.5	1–18	9.9	ttg(ttt)ttt
6	0.5	14–44	6.1	g ⁻ tt(ttt)g ⁻ t
7	0.5	1–28	9.9	ttg(ttt)g ⁻ t

^(a) According to the atom numbering scheme in Figure 1.

TABLE IX. Application of Ward's cluster analysis for OS calculations on 3-ethyl-5,7-dipropyldecane

Step	$\frac{R_v}{\text{nm}}$	Main fragment ^(a)	$\frac{V_T}{\text{kJ mol}^{-1}}$	Conformation
0	–	–	43.3	t(g ⁻)gg(g ⁻)g ⁻ g ⁻ (gg ⁻)tt
1	0.3	20–56	29.6	g ⁻ (g ⁻)gg(gt)tg ⁻ (g ⁻ g ⁻)tt
2	0.2	1–34	26.8	t(g⁻)gt(tt)g⁻g⁻(g⁻g⁻)tt
3	0.3	1–19, 35–56	27.2	t(g ⁻)gt(tt)g ⁻ g ⁻ (g ⁻ g ⁻)tg ⁻
4	0.4	1–19, 35–56	39.4	t(g ⁻)gg(gg ⁻)tg ⁻ (g ⁻ g ⁻)tg ⁻
5	0.2	1–34	39.4	g ⁻ (g ⁻)g ⁻ t(tt)tt(g ⁻ g ⁻)tg ⁻
6	0.35	25–56	39.2	g ⁻ (g ⁻)g ⁻ t(tt)tg ⁻ (g ⁻ g ⁻)tt
0	–	–	43.3	t(g ⁻)gg(g ⁻)g ⁻ g ⁻ (gg ⁻)tt
1	0.5	17–21, 32–56	37.4	t(g ⁻)gg(gt)g ⁻ g ⁻ (tt)tt
2	0.3	1–34	21.9	t(g⁻)gg(gt)g⁻g⁻(g⁻t)tt
0	–	–	36.6	g(g ⁻)tg(gt)g ⁻ t(g ⁻ g ⁻)g ⁻ t
1	0.4	17–21, 32–56	30.3	t(g ⁻)gg(gt)tg ⁻ (g ⁻ g ⁻)tt
2	0.3	1–34	19.5	t(g⁻)gg(tt)g⁻g⁻(g⁻t)tt
3	0.3	22–56	35.3	g ⁻ (g ⁻)g ⁻ t(tt)g ⁻ g ⁻ (g ⁻ g ⁻)g ⁻ t
4	0.4	1–34	40.0	t(g ⁻)gt(tt)g ⁻ g ⁻ (g ⁻ g ⁻)g ⁻ t
5	0.3	20–56	32.3	t(t)gt(tt)g ⁻ g ⁻ (g ⁻ g ⁻)g ⁻ t
6	0.3	17–56	33.4	t(t)gg(tt)g ⁻ g ⁻ (g ⁻ g ⁻)g ⁻ t
7	0.4	17–56	26.8	t(t)gg(gt)g ⁻ g ⁻ (tt)tt
8	0.3	1–34	20.9	t(t)gg(tt)g ⁻ g ⁻ (g ⁻ t)tt
9	0.5	1–31	29.4	t(g ⁻)gg(tt)g ⁻ g ⁻ (g ⁻ t)tt
10	0.5	1–36, 47–49	37.8	t(g ⁻)gg(tt)g ⁻ g ⁻ (tg)tt
11	0.5	17–36	36.9	t(g ⁻)gg(tt)g ⁻ g ⁻ (tt)tt
12	0.3	1–36	29.2	t(g ⁻)gg(tt)g ⁻ g ⁻ (g ⁻ t)tt

^(a) According to the atom numbering scheme in Figure 1.

TABLE X. Application of Ward's cluster analysis for OS calculations, in the stream mode, on *trans*-bis-complexes of *N*-Boc-ACC-OH with copper(II). Fragments 1 and 2 correspond to the first (atoms 1, 2'-33') and second (atoms 1-33) chelate rings, respectively

Step	$\frac{R_V}{\text{nm}}$	Fragment	$\frac{V_T}{\text{kJ mol}^{-1}}$	Conformation ^(a)
<i>(SSR)(SSR)</i>				
0			1579.1	98-98
1	0.3	1	1569.0	98-113
2	0.3	2	1557.8	113-113
3	0.4	1	1555.3	42-97
4	0.5	1	1555.1	40-97
5	0.6	1	1554.2	40-97
6	0.4	2	1557.6	95-97
7	0.3	1	1557.4	95-96
8	0.3	1	1557.4	95-114
9	0.4	2	1555.2	113-41
10	0.5	2	1555.1	40-97
<i>(RSS)(SRR)</i>				
0			1582.9	11-11
1	0.4	2	1582.6	13-11
2	0.5	2	1583.0	35-13
3	0.3	1	1582.8	35-12
4	0.5	1	1583.3	34-11
5	0.4	1	1583.0	34-12
6	0.5	1	1583.3	34-11
<i>(RSR)(SRS)</i>				
0			1588.9	80-80
1	0.4	2	1574.4	49-80
2	0.5	1	1571.4	48-110

^(a) Denoted as in Ref. 24.

TABLE XI. Application of Ward's cluster analysis for OS calculations, in the sieve mode, on *trans*-bis-complexes of *N*-Boc-ACC-OH with copper(II). Fragments 1 and 2 correspond to the first (atoms 1, 2'-33') and second (atoms 1-33) chelate rings, respectively

Step	$\frac{R_V}{\text{nm}}$	Fragment	$\frac{V_T}{\text{kJ mol}^{-1}}$	Conformation ^(a)
<i>(SSR)(SSR)</i>				
0			1579.1	98-98
1	0.6	1	1558.4	53-95
2	0.4	1	1559.6	53-114
3	0.6	2	1555.6	115-95
4	0.4	2	1558.8	60-95
<i>(RSS)(SRR)</i>				
0			1582.9	11-11
1	0.6	2	1579.4	11-65
2	0.5	2	1579.7	35-65
3	0.5	3 ^(b)	1559.7	7-104
4	0.3	2	1558.8	2-104
5	0.3	1	1556.7	2-98
6	0.5	2	1557.9	3-98
<i>(RSR)(SRS)</i>				
0			1588.9	80-80
1	0.4	2	1574.4	49-80
2	0.5	1	1571.4	48-110

^(a) Denoted as in Ref. 24.

^(b) Fragment 3 corresponds to atoms 1, 4-19, 2', 3', 20'-33'; numbering scheme in Figure 1.