

Iterative Method for Finding Low-Energy Conformations Based on the Model of Overlapping Spheres: Application to Alkanes

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A new approximate function for estimation of conformational potential from the excluded volume inside the sphere centered at the geometrical centre of molecule (model of overlapping spheres) is proposed. The value of the function was successfully correlated with the conformational energies of six simple alkanes (from butane to isoheptane). The iterative procedure based on the minimisation of excluded volume is discussed. The method was checked on *n*-decane and five of its branched derivatives (up to C₁₈H₃₈). The method appears to be very efficient in finding the low-energy conformations of normal alkanes but, for branched molecules, it yielded conformations of higher energy in some cases. The method can be regarded as a simple and fast procedure for finding low-energy conformations.

Key words: iterative method, molecular mechanics, excluded volume, low-energy conformations, model of overlapping spheres, alkanes

INTRODUCTION

The problem of finding the global minimum in conformational analysis, *i.e.* the search for the most stable conformer(s), is the central problem of conformational analysis of our times.^{1,2} There are many approaches to the problem; they can be generally classified into three groups: (1) finding the characteristic conformational patterns from experimental data (*e.g.* Ramachandran plot³), (2) building up the final molecular conformation from molecular segments (subconformations),^{4,5} and (3) finding the global minimum

by analysing the potential energy surface (molecular dynamics,⁶ Monte Carlo method,⁷⁻⁹ simulated annealing,¹⁰ low-mode search method¹¹). Recently, approaches based on genetic algorithm have become operational.¹²

Model of overlapping spheres (OS) recently used for estimation of conformational energy¹³ was based on the method proposed by A. J. Hopfinger¹⁴ and H. A. Scheraga¹⁵ for the estimation of hydration (solvation) energy and QSAR analysis.¹⁶ While Hopfinger's model assumes that the solvation energy of a molecule is dependent on excluded volume in a sphere around the solvated atoms in the molecule, my model¹³ assumes that the conformational energy of the molecule is roughly proportional to the excluded volume inside the sphere centered at a specific place in the molecule. This assumption simply rationalises the chemical intuition (less strained conformers are less »crowded«) and therefore the method of overlapping spheres can be regarded as a heuristic approach to the problem of the global minimum. The model proved successful for estimation of conformational energy of copper(II) chelates with *N*-alkylated amino acids,¹³ selecting the conformers with energy difference > 3–5 kJ mol⁻¹.

The OS approach for finding the low-energy conformers has two general advantages: (1) it is computationally simple; calculation of the excluded volume is thousands of times faster than the full energy minimisation (molecular mechanics calculations), and (2) the excluded volume is not very dependent on the exact geometry of the molecule. But the model, as it was originally proposed,¹³ was lacking generality. Namely, it was developed for the very narrow class of molecules (square-planar coordination compounds) and could hardly be applied to other compounds without substantial modifications. The aim of this paper is to propose a more general approach, which should be applicable at least to the acyclic alkanes.

METHODS

The OS approach is based on the evaluation of the function:^{13,14}

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

where V^* is the volume of overlapping spheres, S_v having the radius R_v and the van der Waals sphere s_j of j -th atom, respectively. In the new approach, presented for the first time in this paper, the centre of the sphere is situated at the geometrical centre of the molecule:

$$x_i = 1/N \sum_{j=1}^N x_{ji} \quad i = 1, 2, 3 \quad (2)$$

where the x_{ji} is the i -th coordinate of the j -th atom. Then, a new »conformational potential« is proposed:

$$V_{OS} = k V^* + V_b + V_\theta \quad (3)$$

where k is an energy parameter and V_b and V_θ are bonding and valence angle bending potential, respectively. The value of energy parameter k is not very critical, but it has to be properly chosen to enable rapid convergence without big distortion of bond lengths and angles. Throughout this paper, an arbitrary value $21 \text{ MJ mol}^{-1} \text{ nm}^{-3}$ was used. (Introduction of non-bonded potential in Eq. (3) did not alter the results, but it considerably prolonged the calculations.) Function (3) was subjected to minimisation by the steepest-descent method.

Calculations were performed with a program developed by Kj. Rasmussen and co-workers,¹⁷⁻¹⁹ which was modified to deal with function (3). For molecular mechanics calculations, the simple valence-bond force field for alkanes²⁰ was used.

RESULTS AND DISCUSSION

Analysis of V^ Function*

Excluded volume (*i.e.* volume of overlapping spheres), as defined in Eqs. (1) and (2), was calculated for all conformers of six normal and branched alkanes (Table I) at three values of the sphere radius (R_v). In five cases, the

TABLE I
Conformational analysis of alkanes^a

Molecule	Number of non-equivalent conformers	$\frac{V_{T \max}}{\text{kJ mol}^{-1}}$	$\frac{V_T(V^*_{\min})}{\text{kJ mol}^{-1}}$		
		R_v / nm	0.25	0.30	0.35
<i>n</i> -butane	2	2.5	0.0	0.0	0.0
<i>n</i> -pentane	4	4.6	0.0	0.0	0.0
<i>n</i> -hexane	7	6.0	0.0 ^b	0.0 ^b	0.0 ^b
2-methylbutane	2	2.4	0.0	0.0	0.0
2,3-dimethylbutane	2	0.4	0.0	0.0	0.0
2,3-dimethylpentane	9	12.6	2.5 ^b	2.5 ^b	0.1 ^b

^a V_T , conformational energy; V^* , excluded volume; R_v , sphere radius.

^b Decreasing series of conformational energies does not entirely correspond to the decreasing series of OS volumes.

conformer with the lowest energy (global minimum) had the lowest overlapping volume. In only one case (2,3-dimethylpentane), the minimum of V^* did not correspond to the global minimum of energy, but the conformer with the lowest V^* had an energy $< 2.5 \text{ kJ mol}^{-1}$ above the global minimum. In most cases, decreasing values of conformational potential follow decreasing values of excluded (OS) volume.

The correlation of OS volume with the conformational potential is also visible in the plot of V^* vs. central torsion angle in 2-methylbutane and 2,3-dimethylbutane (Figure 1). For both molecules, the global (*trans*) minimum

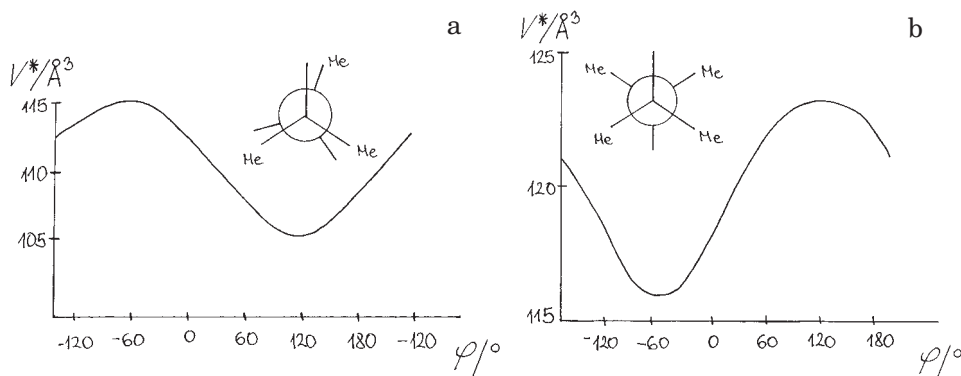


Figure 1. Plot of overlapping volume (V^*) vs. central torsion angle at $R_v = 0.25 \text{ nm}$ for 2-methylbutane (a) and 2,3-dimethylbutane (b).

of conformational potential was obtained after minimising the energy of the conformation with the minimal overlapping volume. The minimum of the V^* function for 2,3-dimethylbutane corresponded to the *trans*-conformation, but for 2-methylbutane the conformation with minimal OS volume was a transition state which, upon minimisation, yielded two equivalent *trans*-conformations.

Iterative Procedure

The first step of the iterative procedure is the steepest-descent minimisation of function (3) starting from an arbitrary conformation (due to simplicity of function (3), this step needs less CPU time than the usual molecular mechanics minimisation). After the first step, a minimisation of total conformational energy is performed (molecular mechanics step). It is not al-

ways necessary to perform MM calculations after the minimisation of function V_{OS} (Eq. (3)); if there was no essential change of conformation, or the obtained conformation was close to an already known conformation or to transition state (very hard to minimise), it is better to change R_v and repeat the procedure. The »global« minimum obtained in the described procedure has to be tested in a full range of R_v values (e.g. 0.20–0.60 nm).

The iterative method was checked on *n*-decane and its four derivatives (Table II). In all (four) runs, the global minimum for *n*-decane (*all-trans* conformation) was obtained in at least five steps, only once changing the central sphere radius ($R_v = 0.50$ nm). Similarly, *n*-hexane yielded the global minimum starting from any conformation after performing one to three cycles of 1000 steepest-descent iterations ($R_v = 0.30$ nm).

The methods did not prove so successful for branched alkanes because conformers of higher energies were also obtained. Moreover, for the highly branched molecule of 3-ethyl-5,7-dipropyldecane it was impossible to obtain more than one minimum of lower energy from any initial conformation. The method seems to be more suitable for more symmetric molecules (compare 4-ethyldecane with 5-butyldecane and 5-butyl-7-propyldecane with 3-ethyl-5,7-dipropyldecane). This finding could be attributed to some kind of conformational heterogeneity of branched molecules, namely to the fact that they are composed of more or less independent, differently »crowded« segments.

Success of minimisation is not dependent on the energy of initial conformation for either kind of alkanes. The global minimum of *n*-decane was obtained in one step starting from a conformer with $V_T = 15.34$ kJ mol⁻¹, but in two steps from a conformer with $V_T = 3.98$ kJ mol⁻¹. The most important factor for the success of the iterative OS method seems to be some kind of conformational flexibility, *i.e.* ability of a conformer to easily change its conformation (by altering up to four torsion angles, in our examples).

To check the influence of sphere radius (R_v) on the course of minimisation, R_v was systematically varied in the range from 0.2 to 0.6 nm (Table III). It is obvious that some conformations of 3-methyldecane (e.g. 2, 5) are more suitable for the iterative approach than others (e.g. 1, 7). Higher values of R_v are generally more efficient than the lower ones. In the 0.55–0.60 nm range, the lowest conformers (14 and 15) are reachable in one step from seven initial conformations (3, 4, 6, 10, 11, 12, and 13). In this range of R_v , no conformers of higher energy were obtained (with the exception of 15), and only in six cases was it not possible to change conformation. However, in the range $R_v = 0.20$ – 0.25 nm, iterative procedure yielded conformers of lower energy only in seven cases.

TABLE II
Global optimisation of *n*-decane and its derivatives^a

	Step	R_v / nm	V_T / kJ mol ⁻¹	Conformation
<i>n</i> -decane				
	0	–	8.37	$g^-g^-g^-g^-g^-g^-$
	1	0.50	4.27	$g^-tg^-tg^-$
	2	0.50	2.65	$g^-tg^-ttg^-$
	3	0.50	0.72	g^-ttttg^-
	4	0.50	-1.73	$tttttg^-$
	5	0.60	-4.18	$tttttt$
	0	–	3.98	$tg^-g^-g^-tg^-g^-$
	1	0.50	3.14	ttg^-tg^-tg
	2	0.50	-4.18	$tttttt$
	0	–	15.34	$tg^-g^-g^-tgg^-$
	1	0.50	-4.18	$tttttt$
	0	–	3.41	$tg^-g^-g^-ttg^-$
	1	0.50	0.54	ttg^-ttg^-
	2	0.50	-4.18	$tttttt$
<i>(S)</i> 4-ethyldecane				
	0	–	21.22	$g^-g^-(t)g^-g^-g^-tg^-$
	1	0.55	6.61	$tg^-(t)g^-g^-g^-tg^-$
	2	0.35	6.33	$tg^-(t)g^-tg^-tg^-$
	3	0.35	5.25	$tg^-(t)g^-tttg^-$
	4	0.55	4.97	$tg^-(g)g^-tttg^-$
	5	0.60	2.61	$tg^-(g)g^-tttt$
	0	–	14.17	$tt(g)g^-tttt$
	1	0.6	11.88	$tt(g)ttttt$
	0	–	8.02	$tt(t)g^-tg^-tg^-$
	1	0.65	5.75	$tt(t)g^-g^-g^-tt$
5-butyldecane				
	0	–	25.33	$g^-g^-g^-(tg^-g^-)g^-g^-gt$
	1	0.60	19.03	$tg^-g^-(tg^-g^-)g^-g^-g^-t$
	2	0.60	5.08	$ttg^-(tg^-g^-)g^-g^-tt$
	3	0.60	3.19	$ttg^-(tg^-t)g^-ttt$

(continued)

TABLE II (cont.)

Step	R_v / nm	V_T / kJ mol ⁻¹	Conformation
4	0.60	0.95	ttg ⁻ (ttt)g ⁻ ttt
0	–	32.66	ttg ⁻ (g ⁻ g ⁻ g ⁻)g ⁻ g ⁻ g ⁻ t
1	0.60	31.13	ttg ⁻ (g ⁻ g ⁻ g ⁻)g ⁻ g ⁻ tt
2	0.60	1.72	ttg ⁻ (g ⁻ tt)g ⁻ g ⁻ t
0	–	59.03	g ⁻ g ⁻ g ⁻ (g ⁻ g ⁻ g ⁻)g ⁻ g ⁻ g ⁻ t
1	0.60	17.98	ttt(g ⁻ g ⁻ g ⁻)g ⁻ g ⁻ tt
2	0.60	10.73	ttt(g ⁻ tt)g ⁻ tg ⁻ t
3	0.60	8.53	ttt(g ⁻ tt)g ⁻ ttt
5-butyl-7-propyldecane			
0	–	33.91	ttg ⁻ (g ⁻ g ⁻ g ⁻)g ⁻ g ⁻ (g ⁻ g ⁻)g ⁻ t
1	0.60	33.32	ttg ⁻ (g ⁻ g ⁻ g ⁻)g ⁻ g ⁻ (g ⁻ g ⁻)tt
2	0.60*	26.50	tg ⁻ t(g ⁻ tt)g ⁻ t(gt)tt
3	0.60	25.11	ttt(g ⁻ tt)g ⁻ t(gt)tt
4	0.60*	23.63	ttt(g ⁻ tt)g ⁻ g ⁻ (tt)tt
5	0.20	17.18	tg ⁻ t(ttt)g ⁻ g ⁻ (tt)tt
6	0.60	16.68	ttt(ttt)g ⁻ g ⁻ (tt)tt
0	–	20.83	ttg ⁻ (gg ⁻ g ⁻)g ⁻ g ⁻ (g ⁻ g ⁻)tt
1	0.60	8.40	ttt(ttt)g ⁻ g ⁻ (g ⁻ g ⁻)tt
2	0.60	7.61	ttt(ttt)g ⁻ g ⁻ (g ⁻ t)tt
0	–	8.02	ttg ⁻ (tg ⁻ g ⁻)g ⁻ g ⁻ (g ⁻ g ⁻)g ⁻ t
1	0.60	6.88	ttg ⁻ (ttt)g ⁻ g ⁻ (g ⁻ g ⁻)tt
3-ethyl-5,7-dipropyldecane			
0	–	39.93	t(g ⁻)tg ⁻ (gt)g ⁻ g ⁻ (g ⁻ g ⁻)tt
1	0.55	33.32	t(g ⁻)tg ⁻ (gt)g ⁻ g ⁻ (g ⁻ t)tt
0	–	43.34	t(g ⁻)gg(gg ⁻)g ⁻ g ⁻ (gg ⁻)tt
1	0.60	30.10	t(g ⁻)gg(gt)g ⁻ g ⁻ (g ⁻ t)tt
0	–	43.04	t(g ⁻)gg(gg ⁻)tg ⁻ (g ⁻ g ⁻)tg ⁻
1	0.60*	23.79	g ⁻ (g ⁻)g ⁻ t(tt)g ⁻ g ⁻ (g ⁻ t)g ⁻ t
0	–	34.38	t(g)gg(gg ⁻)g ⁻ g ⁻ (g ⁻ g ⁻)tg ⁻
1	0.60	23.20	t(g)gg(gt)g ⁻ g ⁻ (g ⁻ g ⁻)tg ⁻
0	–	23.64	t(g)gg(gt)tg ⁻ (g ⁻ g ⁻)tt
1	0.60	23.10	t(g)gg(gt)g ⁻ g ⁻ (g ⁻ g ⁻)tt

^a For meaning of symbols see Table I.

* 2000 steepest-descent iterations were performed, otherwise 1000.

TABLE III

Conformations of (S)3-methyldecane obtained after minimising the V_{OS} function*

No.	$V_T / \text{kJ mol}^{-1}$	R_v / nm								
		0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60
1	17.34	x	x	16	12	11	11	11	11	x
2	9.26	3	4	x	x	<u>17</u>	6	x	5	21
3	9.06	x	x	18	7	19	20	20	15	14
4	6.33	13	10	10	13	13	13	13	15	13
5	6.10	x	x	12	x	8	8	8	8	x
6	5.79	22	10	13	13	13	13	13	13	15
7	5.64	x	x	x	x	x	x	23	24	11
8	5.61	x	x	x	25	25	25	25	9	26
9	4.43	x	x	x	<u>25</u>	12	12	12	12	x
10	3.18	x	x	x	x	<u>27</u>	13	13	15	13
11	3.05	x	28	x	x	x	x	x	14	14
12	2.79	x	x	x	x	x	x	x	15	14
13	1.07	x	<u>10</u>	x	x	x	x	x	x	15
14	0.66	x	x	x	x	x	x	x	x	x
15	0.41	x	<u>29</u>	x	x	x	x	x	x	<u>14</u>

* V_T , strain energy; x, no change of conformation. Conformers with higher energy than initial structure are underlined. Conformations ($V_T / \text{kJ mol}^{-1}$):

1 ttgg⁻g⁻tg⁻, 2 g⁻g⁻g⁻g⁻g⁻g⁻, 3 g⁻g⁻tg⁻g⁻g⁻, 4 g⁻g⁻ttg⁻g⁻, 5 tg⁻g⁻g⁻g⁻g⁻g⁻, 6 g⁻g⁻tg⁻g⁻g⁻, 7 g⁻tttg⁻g⁻, 8 tg⁻tg⁻g⁻g⁻, 9 tg⁻tg⁻ttg⁻, 10 g⁻g⁻ttgt, 11 tttttg⁻, 12 tg⁻tttg⁻, 13 g⁻g⁻tttt, 14 tttttt, 15 tg⁻tttt, 16 ttttg⁻tt (2.95), 17 g⁻gtg⁻tg⁻g⁻ (18.47), 18 g⁻g⁻tttg⁻ (3.45), 19 g⁻ttttg⁻ (6.08), 20 g⁻g⁻tttg⁻ (3.46), 21 tg⁻g⁻g⁻g⁻g⁻t (6.43), 22 g⁻g⁻tttt (1.07), 23 g⁻ttttg⁻ (3.88), 24 tttttg⁻ (3.12), 25 tg⁻tttg⁻g⁻ (4.52), 26 tg⁻tg⁻g⁻g⁻ (5.61), 27 g⁻g⁻ttttg⁻ (3.45), 28 ttttg⁻tt (2.95), 29 tg⁻ttgt (2.77).

CONCLUSION

To perform iterative search for the conformers of lower energy, the following procedure is recommended:

(1) Construct an arbitrary conformation and obtain the local minimum by minimising its strain energy.

(2) Perform 1000 steepest-descent iterations on the conformation, setting up R_v at its maximum value.

(3) If torsion angles were altered, find the minimum of conformational energy starting from this conformation.

(4) If a conformation with lower energy was obtained in step (3), perform again procedures (2) and (3).

(5) If step (3) yielded the conformer of higher energy, or step (2) failed to give a substantial change of torsion angles, repeat procedures (2) – (4), decreasing the R_v value in each step, until the conformer with lower energy is obtained.

Obviously, the iterative OS method may be combined with a random search for initial conformations. Moreover, for systematical application of the method, it is necessary to find the optimal strategy for the studied class of compounds. The drawbacks of the method, *viz.* that the global minimum is not reachable from any conformation and that the minima of higher energies could also be obtained, call for its development. This will be the aim of my further research.

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SAŽETAK**Iterativna metoda za pronalaženje konformacija niske energije temeljena na modelu preklapanja kugli***Nenad Raos*

Predložena je aproksimativna funkcija za procjenu konformacijske energije iz proračuna isključenog volumena unutar kugle smještene u geometrijskom središtu molekule (model preklapanja kugli). Vrijednost te funkcije uspješno je uspoređena s konformacijskim energijama konformera šest jednostavnih alkana (od butana do izoheptana). Prodiskutirana su svojstva iterativne metode utemeljene na minimalizaciji isključenog volumena. Ta je metoda iskušana na *n*-dekanu i njegovim petorim razgranatim derivatima (sve do C₁₈H₃₈). Metoda je vrlo uspješna za pronalaženje konformera niske energije normalnih alkana, ali je za razgranane molekule pokatkad dala konformacije više energije. Predložena iterativna metoda nudi jednostavan i brz postupak za pronalaženje konformacija niske energije.