

Tabu Search Based Strategies for Conformational Search[†]

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This paper presents an application of the new nonlinear global optimization routine *gradient only tabu search* (GOTS) to conformational search problems. It is based on the tabu search strategy which tries to determine the global minimum of a function by the *steepest descent–modest ascent* strategy. The refinement of ranking procedure of the original GOTS method and the exploitation of simulated annealing elements are described, and the modifications of the GOTS algorithm necessary to adopt it to conformation searches are explained. The utility of the GOTS for conformational search problems is tested using various examples.

1. Introduction

Efficient searches for global minima of highly dimensional functions¹ with numerous local minima are central for the solution of many problems in computational chemistry. Well known examples are the optimization of force-field parameters or the determination of possible reaction paths between reactants and products.^{2–4} The identification of the energetically lowest lying conformers of molecules possessing a high number of freely rotatable bonds is another important global optimization problem in computational chemistry.^{5,6} These conformers are important, since they determine most molecular properties at room temperature.^{7–12}

Mathematically, such a conformational search represents a global optimization problem in which the potential energy function of the molecule is the objective function while the coordinates, that are used to represent the conformation of the molecule, are the variables. The perfect global optimization routine would always give the shortest way from a given starting point to the global minimum. For the potential energy surface (PES) of a molecule, this way includes downhill and uphill moves. While the best downhill moves can be well approximated as the shortest way to the next local minimum, the uphill moves are less straightforward, since the direction to the global minimum is not known in advance. For smaller molecules, the global energy minimum and the lowest lying minima can be determined systematically.^{13,14} One possibility is to choose a large number of starting conformations that are equally distributed on the energy surface. From each of them, a minimization to the nearest minimum is performed using local optimization techniques and then all duplicated structures are rejected.¹⁵ With an increasing number of freely rotatable single bonds, however, the search space increases strongly with the number of degrees of freedom (e.g., torsion angle), which is typically proportional to the size of the molecule. This is known as *combinatorial explosion*.¹⁶ Therefore, to obtain the energetically low lying conformations at tractable computational cost, specialized conformational search algorithms are needed. Over the past several years, a multitude of conformational search techniques have been developed for this purpose,^{17–23} each with its

particular strengths and weaknesses. Reviews about commonly used techniques, such as classical molecular dynamics simulation (MD),^{24,25} mutually orthogonal Latin squares (MOLS) conformational search technique,²⁶ smoothing/deformation²⁷ and systematic search methods,^{28,29} Monte Carlo,³⁰ simulated annealing,^{31,32} and genetic algorithms,³³ can be taken from the literature.^{34–36}

In the present paper, we utilize a variant of the tabu search (TS) for conformational search. The TS^{37–39} is a metaheuristic^{40–43} which employs the “steepest descent–modest ascent” strategy. The steepest descent is taken to find the next local minimum, while the modest ascent path is followed to escape a local minimum and to search for the next local minimum. Reverse modes and cycles are prevented by the use of a *tabu list* (TL) which sets already visited solutions tabu. The TL also recognizes if the search gets stuck in a given region. In such cases, a diversification search (DS) is performed which guides the search to different and hopefully more promising regions of the search space. For many applications in a wide variety of fields, the TS yielded much better solutions than methods previously applied.^{44–49}

An adaptation of the used algorithm to the computational chemistry problems mentioned above is not straightforward, since, for example, conformational searches or the optimizations of force field parameters represent continuous optimization problems. Nevertheless, several attempts have been made to deal with continuous optimization problems.^{50–61} We developed three different approaches, the gradient tabu search (GTS),⁶² the gradient only tabu search (GOTS),⁶³ and the tabu search with Powell’s algorithm (TSPA).⁶³ The GTS algorithm uses analytical gradients for a fast minimization to the next local minimum and the diagonal elements of the analytical Hessian to escape local minima. For the minimization, a combination of the steepest descent and the quasi-Newton methods is used.^{64–67} To follow the modest ascent, the diagonal elements of the Hessian are employed. To determine the direction, they are weighted by a linear ranking procedure. For the tabu list, concepts as tabu directions (TD) and tabu regions (TR) which are related to previous ideas of Glover⁶⁸ were used to ensure an efficient blocking of already visited regions. GOTS and TSPA were developed to avoid the computation of Hessian and also of gradients, respectively. To determine the next local minimum (local minimization part), the GOTS uses the same strategy as

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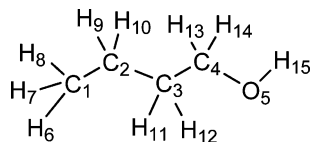


Figure 1. Atom numeration of the *n*-butanol molecule.

the GTS, but to escape a local minimum via the modest ascent, only a grid of function evaluations is employed. The TSPA uses the same method for the modest ascent strategy as the GOTS, but Powell's algorithm is employed for the steepest descent part. Due to the different strategies, the TSPA only needs functional evaluations but no gradients or Hessians, while the GOTS only requires gradients. All other concepts used within the GOTS and the TSPA were taken from the GTS. Numerical results for the GTS and GOTS methods, which are available in ref 63, showed that these approaches are more efficient than previous global optimizers. For functions with higher dimensionality, the GOTS becomes more efficient than the GTS. The efficiency of the TSPA method is comparable to that of genetic algorithms.^{69,70}

In the present paper, the GOTS has been adapted for conformational searches. To increase the efficiency of the optimization, our first ansatz has been combined with simulated annealing elements.^{71–74} The method was implemented into the computational chemistry environment ChemShell, and test computations have been performed for lysine and arginine, two ACE (angiotensin converting enzyme) inhibitors, 2-acetoxy-*N,N,N*-trimethylethanaminium (acetylcholine), and an HIV-1 protease inhibitor. The paper is organized as follows. In section 2, various details of the used algorithms are described. Then, suitability of the new approach is tested using some examples. It is described in section 3. Conclusions complete the work.

2. Adaptation of the GOTS Algorithm for Conformational Search

The choice of the coordinates used to describe a molecule is critical for the efficiency of the optimization.⁶³ Since gradients and Hessians are usually calculated in Cartesian space, Cartesian coordinates would be the most straightforward choice. However, transitions from one conformer to another one are mainly accompanied by variations in dihedral angles, while bond distances and angles change only slightly. To exploit this difference in the stiffness, we employed nonredundant internal coordinates and varied only the dihedral angles to escape a local minimum. During minimization to the next local minimum, all coordinates are optimized. The nonredundant coordinates were represented in the *Z*-matrix formalism employed in the Gaussian program package.⁷⁵

Often, various dihedral angles have to be changed together to perform proper rotations around a given single bond. For example, to rotate a terminal methyl group of the *n*-butanol molecule (see Figure 1) consisting of atoms C₁H₆H₇H₈ around the C₁C₂ axis, it is necessary to modify three dihedral angles (C₃C₂C₁H₆, C₃C₂C₁H₇, C₃C₂C₁H₈) at the same time.

According to Chass⁷⁶ or Echenique and Alonso,⁷⁷ such proper rotations can be assured by dividing the dihedral angles into *main* and *dependent torsions*.^{78,79} Hence, during the modest ascent part, only the main torsions are independently varied, while the dependent torsions are modified accordingly so that proper rotations take place. To find the next local minimum, all internal coordinates (distances, angles, and dihedral angles) are again independently optimized. The algorithm used to determine main and dependent dihedral angles is depicted in Figure 2.

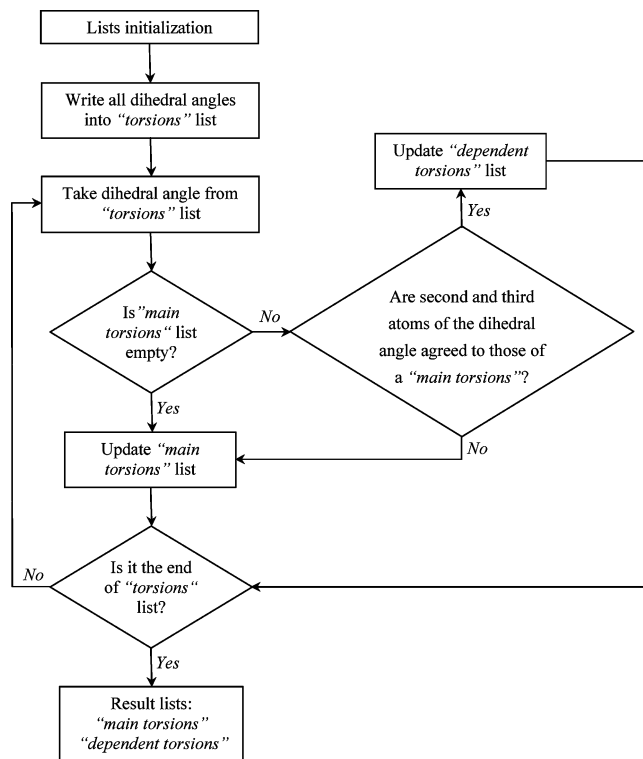


Figure 2. Flowchart of the determination of main and dependent torsion angles.

During the modest ascent search, the GOTS algorithm uses only function evaluations to escape a local minimum. At the local minimum, all functional values Fz_i^+ and Fz_i^- (eq 2) are computed with single-point calculations to determine the general direction of the following moves. They are obtained by varying each dimension by a user defined step size Δx_i^0 . In our previous approach, the direction in which the search is moved is estimated according to⁶²

$$x_i^{\text{new}} = x_i^{\text{old}} + \Delta x_i^0 \times \text{rank}_i \quad (1)$$

$$\begin{aligned} Fz_i^+ &= F(x_1, x_2, \dots, x_j + \Delta x_j^0, \dots, x_{\text{NDIM}}) \\ Fz_i^- &= F(x_1, x_2, \dots, x_j - \Delta x_j^0, \dots, x_{\text{NDIM}}) \end{aligned} \quad (2)$$

$$D_i = \begin{cases} +, & \text{if } Fz_i^+ < Fz_i^- \\ -, & \text{if } Fz_i^+ > Fz_i^- \end{cases} \quad (3)$$

$$Fz_i = F(x_1, x_2, \dots, x_j + D_j \times \Delta x_j^0, \dots, x_{\text{NDIM}}) \quad (4)$$

$$\text{rank}_i = \text{rank}_{\text{min}} + (\text{rank}_{\text{max}} - \text{rank}_{\text{min}}) \left(\frac{Fz_{\text{min}} - Fz_i}{Fz_{\text{max}} - Fz_{\text{min}}} \right) \quad (5)$$

Here, x_i denotes the *i*th coordinate. In our previous approach, the coefficients rank_{max} and rank_{min} were set to 0 and 1. However, for the conformational search, the computed energy differences were found to be too small to obtain reasonable ranking coefficients rank_i . Hence, the coefficients rank_{max} and rank_{min} are calculated for each case separately:

$$\text{rank}_{\min} = 2 - \frac{Fz_{\max}}{Fz_{\min}} \quad \text{if } Fz_{\max} < 2 \cdot Fz_{\min} \quad (6)$$

$$\text{rank}_{\min} = 0.1 \quad \text{otherwise}$$

To calculate rank_{\max} , the same percentage analysis as for rank_{\min} is made for each value:

$$\text{rank}_{\max} = 2 - \frac{Fz_i}{Fz_{\min}} \quad \text{if } Fz_i < 2 \cdot Fz_{\min} \quad (7)$$

$$\text{rank}_{\max} = 1.0 \quad \text{otherwise}$$

The resulting modest ascent is followed until the next calculated function value is smaller than the previous one. This indicates that the barrier to the next valley is crossed. From this point, the next local minimum is located using the local minimization routines.

Reverse moves and cycles were avoided by the tabu list (TL) concept as used previously. For the conformational search, however, only tabu regions (TR) could be employed, since tabu direction (TD) turned out to be incompatible. A diversification search (DS) is performed if the search gets stuck in an unpromising area. For the conformational search, this is performed if the solution does not improve after a given number of new local minima (parameter BADMAX, see Table 1) or if all neighborhood solutions of the local minimum under consideration are already set tabu. To ensure that the search switches to regions that were not already investigated in the DS, the main torsions are changed in steps of 60° (parameter diversification step, see Table 1) and the dependent torsions are moved accordingly. The rest of the variables are kept constant. After excluding all points which belong to an already established TR, the new search starts from the point with the lowest energy value.

To include more probability aspects, ideas from the simulated annealing (SA) method have been implemented into the GOTS. They shall help to focus on promising areas of the large search space. In our approach, the SA ideas are exploited to determine if a new minimum is taken as the new starting point or not. If the new minimum is lower in energy, it is always taken. If it is higher than the previous one, the Metropolis criteria⁸⁰ is used to decide if it is nevertheless taken as the new starting point. If the new minimum is not accepted, the algorithm returns to the previous minimum and continues the search along the next modest ascent direction. This SA element directs the search to more promising areas. If the next local minimum is very high, the search concentrates on the region around the last minimum which is considerably lower in energy. The flowchart given in Figure 3 depicts the GOTS approach to the conformational search.

The GOTS possesses some user-defined parameters which are summarized in Table 1. The parameter Δx_i gives the step size during the modest ascent search. One could assume that small step sizes increase the accuracy. However, this is misleading, since the energy differences between the directions get so small that the ranking procedure does not work properly anymore. On the basis of our experiences, $\Delta x_i = 45^\circ$ is recommended as a standard value. With larger step sizes, the average number of steps needed to leave a local minimum decreases but sometimes minima are missed.

In our previous GOTS version, a diversification search is started if the solution does not improve after BADMAX local minima. As in previous versions of the GOTS, BADMAX was

TABLE 1: Description of the Parameters of the GOTS Application to the Conformational Search

parameter	purpose	recommended values
Δx_i	step size at the modest ascent strategy	45°
BADMAX	number of not improved minima after which a DS is performed	5
diversification step	step size used during the diversification strategy	60°
rank_{\max}	default maximum recency ranked value	1.0
rank_{\min}	default minimum recency ranked value	0
TR	$1/2$ of the tabu region diameter	10°
T	control parameter (analog of temperature)	150 kJ mol^{-1}

set to 5, but in the present version, this hard rule is modified by the Metropolis criterion for which the parameter T is used. In these first test cases, T is set 150 kJ mol^{-1} . With such high T values, the probability that high lying minima are taken as the new starting structure is also high. Hence, this setting ensures that also high lying minima are used as new starting points. This is necessary to overcome high lying regions and to move to complete different regions. With lower T values, the GOTS could get trapped in the given region. The value of T is decreased by 10% for each newly found minimum which is higher in energy.

The parameter TR controls the size of the tabu regions within the whole optimization process. One would expect that small TR do not efficiently block already visited regions so that the effort decreases with increasing TR. However, in most cases, the effort increases for larger TR. This counterintuitive behavior may result because the tabu regions become so large that minima lying close by already visited points are overlooked or because the optimal path to the global minimum is blocked. A value of $\text{TR} = 10^\circ$, however, seems to be a good choice for a large variety of different problems.

3. Applications

To study its suitability for conformation searches, the modified GOTS was applied to conformational studies for lysine,

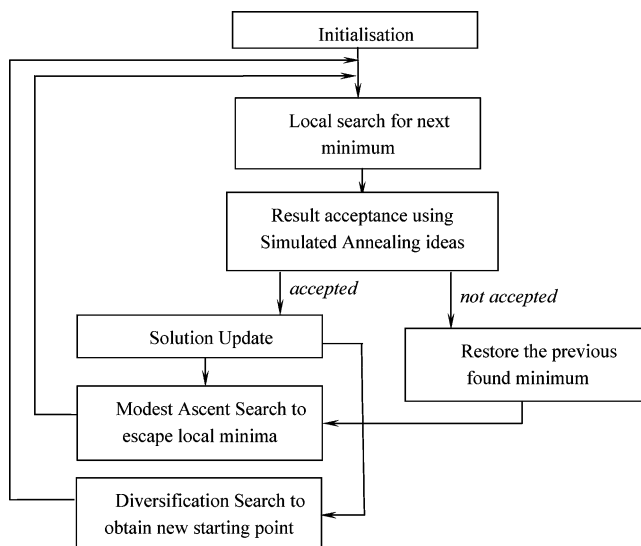


Figure 3. Flowchart of GOTS with SA elements.

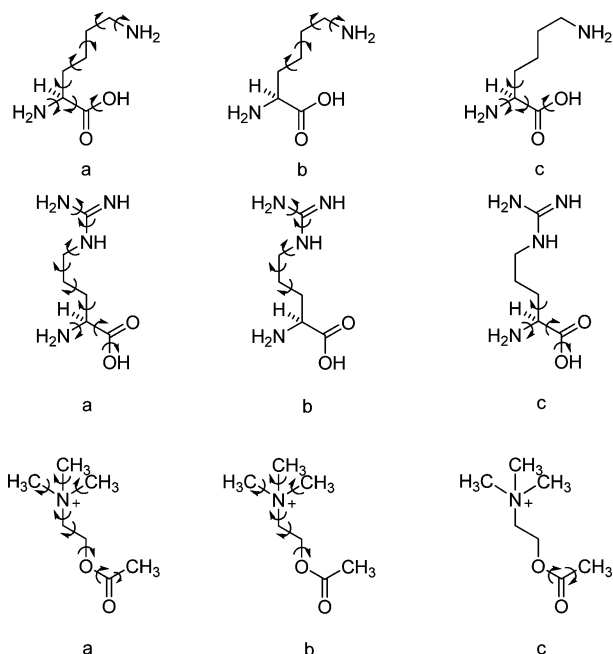


Figure 4. Main torsions of lysine (upper part), arginine (middle part), and acetylcholine (lower part) and their subdivision used in the divide-and-conquer (DaC) strategy.

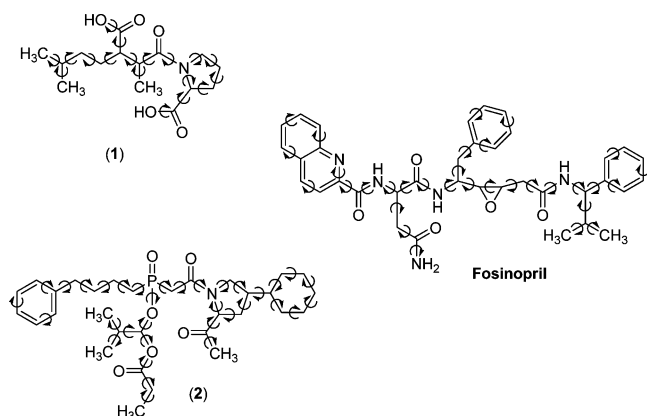


Figure 5. Main torsions of the ACE inhibitor **1**, Fosinopril, and the HIV-1 protease inhibitor **2**.

arginine, 2-acetoxy-*N,N,N*-trimethylethanaminium (acetylcholine), the ACE inhibitor **1**, Fosinopril which represents another ACE inhibitor, and the HIV-1 protease inhibitor **2**. All computations were performed within the ChemShell environment running under Linux. For the calculations, the universal force field (UFF)⁸¹ was employed. Lysine has 66 internal degrees of freedom which can be built up with 21 dihedral angles. According to our approach, these dihedral angles are subdivided into 8 main torsions and 13 dependent torsions. Hence, during the modest ascent part (escape from a local minimum) for lysine only 8 torsions are varied while all internal degrees of freedom are optimized within the local minimization part (finding the next local minimum). The corresponding numbers of main torsions are 11 for arginine, 8 for acetylcholine, 17 for the ACE inhibitors **1**, 34 for Fosinopril, and 41 for the HIV-1 protease inhibitor **2**. They are indicated in Figures 4 and 5.

Let us first concentrate on the smaller molecules lysine, arginine, and acetylcholine. The main torsions of lysine are indicated in Figure 4a (upper panel). To test how divide-and-conquer (DaC) strategies⁸² accelerate the convergence of the GOTS, the main torsions were further subdivided into those

TABLE 2: Test Results for Lysine, Arginine, and Acetylcholine^a

molecule	start structure	first ^b	lowest ^c		
			normal	DaC	
Lys	1 ^d	1323 ^e	13	0.3	0.0
	2	486	13	0.8	0.0
	3	306	7	0.0	0.0
	4	399	8	0.0	0.0
Arg	1 ^d	1452	58	2.9	0.0
	2	1398	49	6.3	0.5
	3	1385	44	5.5	0.0
	4	1892	49	9.2	1.8
acetylcholine	1 ^d	309	24	0.0	0.0
	2	716	19	0.0	0.0
	3	4735	19	0.0	0.0

^a All energies are given with respect to the energetically lowest minimum (kJ mol^{-1}). ^b First minimum found in the conformational search. ^c Lowest lying minimum found in the conformational search. ^d Structures obtained from starting structure 1 are illustrated in Figures 6–8. ^e Energies relative to the lowest minimum.

connected with the residue (Figure 4, upper panel b) and those connected with the backbone part, i.e., the carboxylic acid, the ammonium, and the α -carbon center (Figure 4, upper panel c). The subdivision of the main torsions of arginine and acetylcholine is also indicated in Figure 4 (middle and lower parts). In the DaC run, the conformational search starts with the smaller part. Then, the best solution is kept constant within the modest ascent part of the consecutive search. During the local minimization part, again all internal coordinates are optimized without any restriction. Since within the local minimization part all internal degrees of freedom are optimized, the first minimum found in the normal approach (no subdivision of main torsions) is the same as that found within the DaC strategy.

The results for the smaller molecules are summarized in Table 2. The runs were started independently from different structures to test the stability of the GOTS. Table 2 gives the energies of the starting structures, of the first minimum encountered in the GOTS, and of the lowest lying structures found in one GOTS run. All energies are given relative to the lowest minimum found in the all GOTS performed for the molecule. The structures found in the GOTS which started from start structures 1 are illustrated in Figures 6–8. Finally, Figure 9 monitors the progression of conformational search starting from start structures 1.

Results show that despite similar sizes lysine and acetylcholine seem to represent easier examples than arginine. For the former, the lowest lying minimum is found independently of the starting structure, although for lysine the DaC strategy seems to be favorable in comparison to the normal approach (no subdivision of main torsions). Figures 9 and 10 show additionally that the GOTS in the present form indeed scans large parts of the phase space and is able to locate low lying as well as high lying minima. For lysine, the energies of the detected minima vary over a range of 100 kJ mol^{-1} . For acetylcholine, the energies of the detected minima alter in a range of 25 kJ mol^{-1} . Please note that the tabu list (TL) impedes that the same minimum appears twice in Figure 9; i.e., despite very similar energies, all minima correspond to different conformers (e.g., minima 23–26 for lysine or minima 10, 12, 14, 15, etc., for acetylcholine). This indicates that the GOTS is also able to find energetically close lying minima which is, for example, of interest for the determination of Boltzmann-weighted ensembles.

All results show that arginine represents a more difficult example than lysine or acetylcholine. In all cases, very low lying

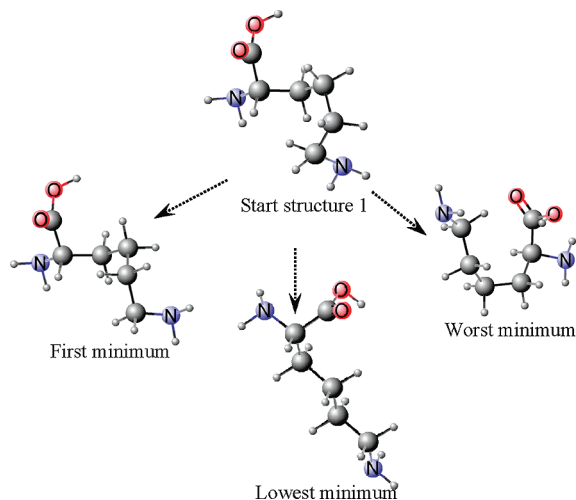


Figure 6. Illustration of the structures characterized in Table 2 for lysine.

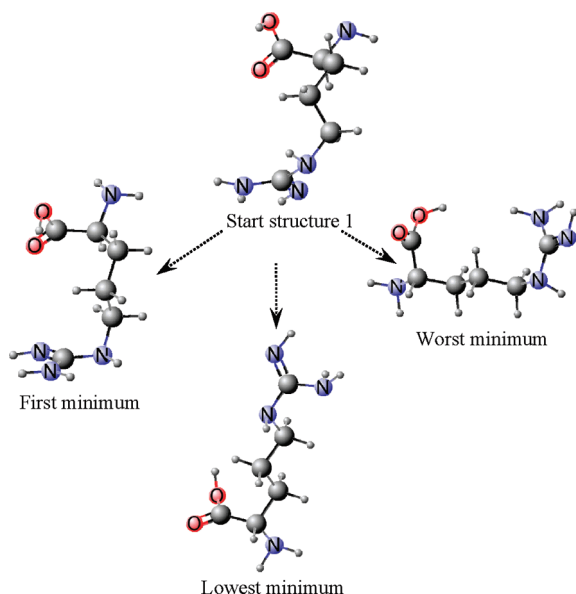


Figure 7. Illustration of the structures characterized in Table 2 for arginine.

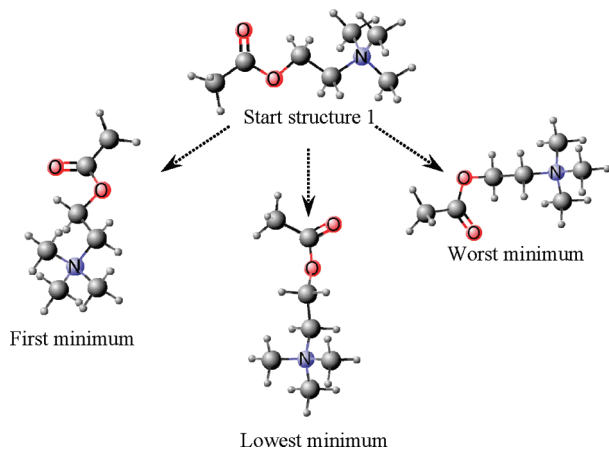


Figure 8. Illustration of the structures characterized in Table 2 for acetylcholine.

minima are detected; however, the apparent global minimum is only found if the DaC strategy is used. Figure 9 also shows that during the GOTS run high lying minima are encountered more often than for lysine or acetylcholine. Nevertheless, the

TABLE 3: Test Results for the Larger Molecules^a

molecule	start structure	first minimum	lowest minimum
Fosinopril	676	47	0
1	758	29	0
2	665	74	0

^a All energies are given with respect to the energetically lowest minimum (kJ mol^{-1}).

energies of the detected minima vary in the same range as for lysine (70 kJ mol^{-1}).

To test the suitability of our approach for larger molecules, conformational searches were also carried out for Fosinopril, the ACE inhibitor **1**, and the HIV-1 protease inhibitor **2** (Figure 5). DaC strategies were also tested for these molecules, but with or without such strategies, the same global minimum was detected and also the convergence of the conformational search was about the same. Since the DaC tests did not differ considerably from the normal approach, Table 3 only gives the results of the normal approach. Figure 11 gives the geometrical arrangements of the starting structure and of the first and lowest lying conformer found for **1**, and Figure 10 shows the progression of the corresponding conformational search.

The results obtained for the larger molecules show that also for larger molecules the GOTS is able to locate various local minima with quite different nuclear arrangements and quite varying energies. As found in previous applications, the GOTS very fast leads to solutions close to the global minimum but is also able to scan large parts of the phase space. Important for

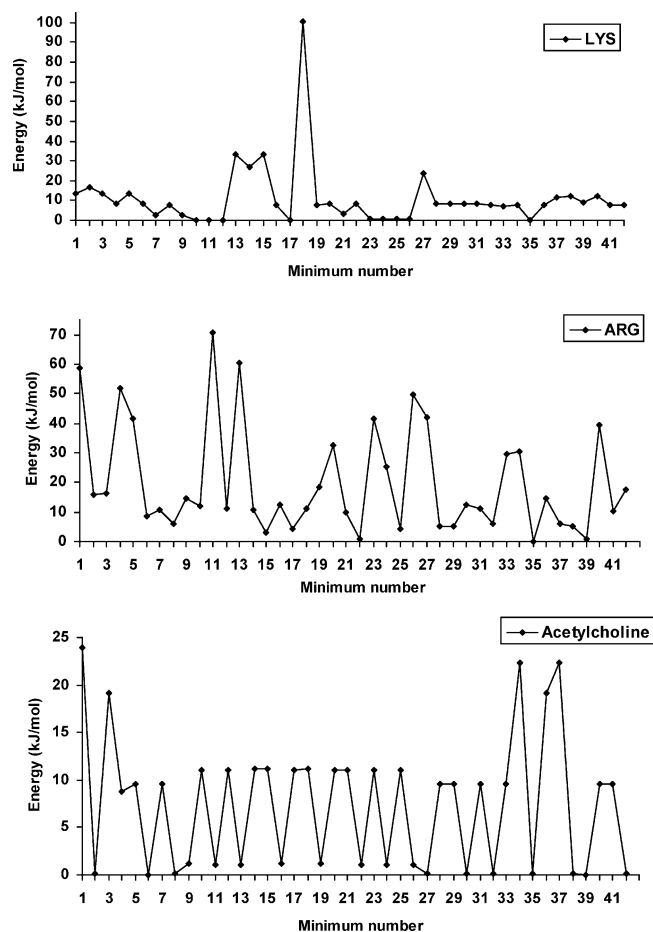


Figure 9. Progression of conformational search starting from start structure 1.

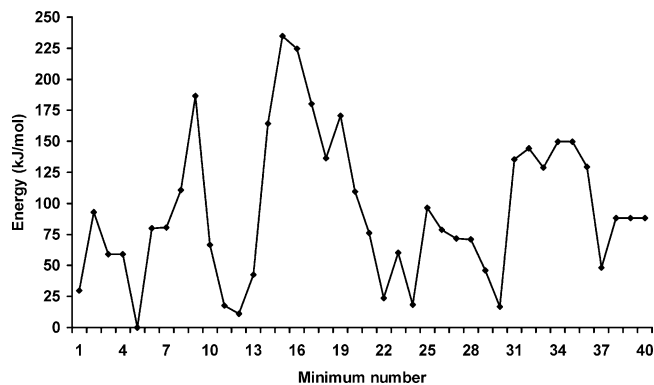


Figure 10. Progression of conformational search for the ACE inhibitor 1.

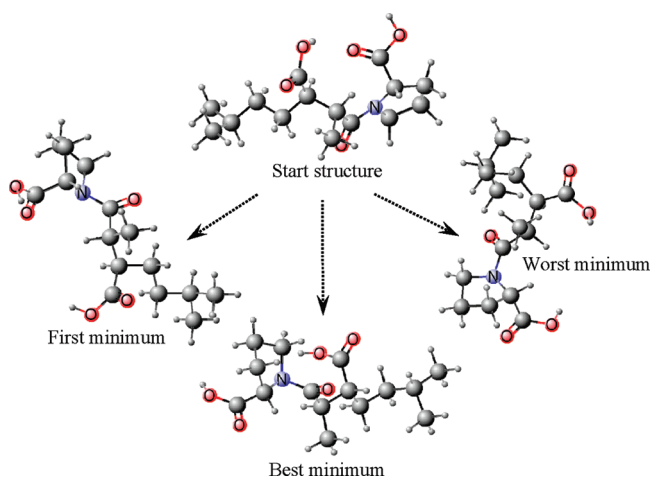


Figure 11. Illustration of the structures characterized in Table 3 for 1.

this is the ability of the GOTS to surmount high lying regions as for example shown in Figure 10 for compound 1 (minima 12–22).

4. Conclusions and Future Work

In this paper, the global optimization routine called gradient only tabu search (GOTS) was adapted and applied to conformational search problems. The paper describes various algorithmic details, such as refinement of ranking procedure of the original GOTS method, the definition of the variables, and the exploitation of simulated annealing elements. Parameters of the approach are discussed, and appropriate values are recommended. To test the suitability of the approach for conformational search, various molecules of differing size are used as test cases. The results indicate that the GOTS is able to detect the low lying minima of molecules with a high number of freely rotatable single bonds, since its strategy directs the search to low lying parts of the potential energy surface. Nevertheless, since higher lying minima are also accepted, the search is also able to surmount high lying parts. This ability makes the GOTS less dependent on the starting structure, since it enables the traverse of high lying regions which separate two low lying ones with quite differing nuclei arrangements. Future work will concentrate on algorithms which provide promising starting structures, e.g., conformations which are stabilized by internal hydrogen bonds.

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Supporting Information Available: Figures showing structures of Fosinopril and HIV-1 protease inhibitor. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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