

The UTN program

computing interconversion energy between conformers in acyclic molecules

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Abstract

We give an algorithm which goal is to find the energy barrier between a given pair of points in a graph which represents the conformational space of a molecule.

If the conformational space is homeomorphic to an n -dimensional torus, then the graph can be chosen of a particular form. The UTN software, which implements the algorithm in this case, is described in detail.

Finally we focus on applications: to show how UTN works, some examples are carried on in detail, with the additional support of a graphical animation in the two-dimensional case.

The source code of the program and some data of the examples are available to the reader.

Keywords: Conformers; energy barrier; systematic conformational search; acyclic-molecules, transition state.

Introduction

The analysis of the conformational behaviour of a molecule is of fundamental importance to study, for example, structure-activity relationships in compounds having biological activity, or to interpret and understand experimental results (e.g. NMR spectroscopic data (Mierke, Kurz & Kessler 1994; Burgess, Ho & Pettitt, 1995)).

An exhaustive conformational analysis requires three fundamental steps: obtaining a collection of conformations, localising the energy minima (conformers) on the potential energy surface and, finally, computing the energy barrier for the conformers' interconversion. In the last years a lot of different algorithms have been developed to explore the conformational space accessible to both cyclic and acyclic molecules. The investigation methods that are at the base of these latter algorithms span between the grid search, the molecular dynamics, the distance geometry and the Monte Carlo techniques (Leach, 1991; Van Gunsteren & Berendsen, 1990; Howard & Kollman, 1988; Wiberg & Boyd, 1972; Lipton & Still, 1988; Goodman & Still, 1991; McAmmon & Harvey, 1987; Crippen & Havel, 1988; Weiner et al., 1983; Crippen, 1992; Chang, Guida & Still, 1989; Weinberg & Wolfe, 1994). Each one of these methods has strengths and weaknesses. The so-called "Stochastic techniques" (i.e. molecular dynamics, distance geometry and Monte Carlo methods), for example, are suited for a large class of molecule types, but require long computations to ensure a complete examination of the conformational space. However, to save computational time, they can better be used in combination with some additional methods which are more useful for local analysis of the conformational space.

On the other hand, "deterministic search methods" (like systematic variation of torsion angles) are the only ones which provide the certainty to find all the conformations in a given grid; however, they require a lot of computational time. In fact, considering N dihedral angles to be investigated in the specimen, if each torsion angle takes p values there will be p^N energy values to compute. Therefore, the computational complexity of the algorithm is exponential in the number of rotatable bonds. Our opinion is that this problem is not an insurmountable difficulty, because nowadays in a very short time is possible to perform some computations that ten years ago would have needed days or months. Moreover, the preliminary computation of energy values – which represent the most time-consuming activity in our approach – can be done separately for each conformation, thus being compatible with parallel computing techniques which enable to reduce drastically the total computational time.

The second step is devoted to the determination of the minima on the potential energy space; the most used methods to determine the conformers of a molecule are the minimization of some given conformations and the simulated annealing. The first of these methods is able to find conformers minimizing the energy of all the conformations to their nearest minimum. Minimization algorithms are based on gradient descent approach, so we can say that they head "down-hill" toward the nearest minimum. This implies that "far" minima aren't reachable using such algorithms, because it could require some period of "up-hill" movement. The second method is used with molecular dynamics or Monte Carlo computations. In a first step the system being studied is heated and held at a certain high temperature, in order to let the molecule explore efficiently the whole conformational space; then the system is carefully cooled in the attempt to find all the energy minima.

The third fundamental step about the conformational investigation of a molecule con-

cerns the determination of the energy interconversion barrier. One of the first methods used to compute the energy of the transition state has been based on the minimization of the gradient norm (McIver & Komornicki, 1972; Komornicki et al., 1977), or of the energy (Poppinger, 1975). One important problem in using this method is the lack of certainty about the convergence to a transition state; in fact, this algorithm converges to a zero of the potential gradient, which could as well be a minimum. In the last years a lot of different algorithms targeted to determine transition states have been developed (Fisher & Karplus, 1992; Berry, Davis & Beck, 1988; Bell, Crighton & Fletcher, 1981; Cerjan & Miller, 1981; Muller & Brown, 1979; Halgren & Lipscomb, 1977; Mezey, Peterson & Csizmandia, 1977). One of the main problems of some of these methods is that they are usable only for system with few atoms (McIver & Komornicki, 1972; Komornicki et al., 1977; Poppinger, 1975; Cerjan & Miller, 1981; Muller & Brown, 1979; Halgren & Lipscomb, 1977; Mezey, Peterson & Csizmandia, 1977).

The algorithms which are at the base of these different methods span between the conjugate gradient method in conjunction with the quasi-Newton one (Bell et al., 1981) and the conjugate peak refinement (Fischer & Karplus, 1992). Some of them make use of molecular dynamics, like for example the method proposed by Berry, Davis and Beck (1988).

Here is necessary to make a general remark about this third step. Considering the non-local nature of the energy barrier computation, it is not difficult to understand that non-exhaustive methods give only an upper bound for the energy barrier, because they cannot exclude the existence of another path along which the energy barrier is lower than the one they compute. So we preferred the exhaustive approach, in spite of the large amount of computational resources that it requires. Moreover, the fact that we are approximating the problem with a finite (and thus coarser) graph can often be a non-removable limit of the context in which the analysis takes place, e.g. when working with experimental sample data, which is *a priori* limited.

The program we present in this paper (UTN) allows to determine the conformers in the potential energy space, and to compute the interconversion energy barrier between a selected pair of minima by locating the involved transition state. UTN needs some preliminary work: given a molecule which has some rotatable bond – whose geometry, relatively to its bond distance and angles, has been optimized – the torsional space is explored exhaustively by means of a systematic search procedure. The resulting set of conformations is then minimized, and a file is produced where each isomer is sorted by the corresponding energy value and by the values of its dihedral angles; this file, together with a brief configuration file, is the correct input for the UTN software.

Finally, we observe that this software, although here presented in the particular context of conformational analysis of molecules, can be used in general to find energy barriers in any problem in which there is a potential energy defined over a topological space homeomorphic to a product of circles and (after some trivial modifications to the software) of segments.

Statement of the problem and description of the algorithm

To begin with, we recall some standard mathematical notations. A *graph* is a pair $G = (V, E)$; the elements of V are called “vertices” or “points”; E is a set which elements are unordered pairs of vertices, called “edges”. Two points v, w are said to be *adjacent* if and only if $\{v, w\} \in E$. For any subset $W \subset V$, the *adjacency of W* is

the set $\text{adj}(W)$ of all the points $z \notin W$ that are adjacent to a point of W . Finally, we assume that in this paper we will deal only with *finite* graphs, i.e. that V (and hence E) are assumed to be finite sets.

The input data is essentially composed by the pair “space-energy”, respectively the graph $G = (V, E)$ and the function $U : V \rightarrow \mathbb{R}$; the user also has to specify two points v_1, v_2 between which the energy barrier is computed.

To state the problem, we need the following definition.

definition 1. a *path* γ in G is a sequence of points x_1, \dots, x_n such that each x_i is adjacent to x_{i+1} , for $i = 1, \dots, n - 1$.

γ is said to be an *L-path* if $U(x) \leq L$ for all $x \in \gamma$.

γ is said to *join* its two endpoints x_1 and x_n .

Intuitively speaking, an *L-path* is a path along which the energy is bounded from the above by L .

Consider now the following problem:

problem 1 (finding the barrier). Given two points $x, y \in V$, find the minimum value $L \in \mathbb{R}$ such that there exists an *L-path* γ , joining x with y .

definition 2. Such L is the energy barrier between x and y .

Using the concept of *L-pathwise* connected components, the barrier-finding problem can be stated in a form that is equivalent, but more fit for the purpose of the description of the algorithm.

definition 3. For any $L \in \mathbb{R}$ and $x \in V$, we define

$$V(x, L) := \{ z \in V \mid \text{there exists an } L\text{-path joining } x \text{ with } z \} .$$

We refer to $V(x, L)$ as the *L-pathwise connected component of X that contains x*.

The above problem can thus be formulated in the following alternate way:

problem 2 (finding the barrier, alternate formulation). Given two points $x, y \in X$, find the minimum value $L \in \mathbb{R}$ such that $y \in V(x, L)$.

remark 1. The finiteness of G implies trivially that such minima always exist. Also, it is easily seen that both the former statement and the latter one are equivalent, i.e. with the same input data they have the same solution. (This is immediately proved by noting that $L_{\text{former}} \leq L_{\text{latter}}$ and that the strict inequality would lead to an absurd.)

Now we describe the algorithm, which follows closely the alternate formulation of the problem. C is a real variable that will change its value during the computation, starting from $U(x)$ and gradually increasing until it takes the value of the barrier. At each step, the algorithm will travel V along the edges, marking the points that have been “visited”, until it reaches y . We will denote with M the subset of V composed by marked points, which plays the role of $V(x, L)$ as L increases.

1. mark the point x and set $C := U(x)$.

2. if $y \in M$, then the algorithm ends; the current value of C is the barrier between x and y .
3. if there is a point $z \in \text{adj}(M)$ such that $U(z) \leq C$, then mark z and go to step 2;
4. let z be a minimum for the energy U in $\text{adj}(M)$; set $C := U(z)$, mark z and go to step 2.

proposition 1. *The algorithm stops after a finite number of steps. Moreover, the final value of C is equal to the solution L of the above stated problem.*

Proof. The algorithm proceeds by initially setting $V = \{x\}$ and then sequentially executing the described steps, going back to step 2 until the stop condition becomes true. But just before the jump to step 2, the set M is enlarged by the adjunction of a new point z . Being M a subset of the finite set V , after at most $|V| - 1$ jumps the algorithm stops because y belongs to M .

$L \leq C$ holds, because $y \in M$ and $M \subset V(x, C)$. Indeed, this last condition is trivially true at the beginning and it is easily seen to be preserved at each step of the algorithm.

But also $C \leq L$. Observe that the only choice for C to be changed is in step 4, and initially $C = U(x) \leq L$. So we only need to show that at step 4 C cannot be set at a value greater than L .

Suppose by contradiction that at a certain moment the algorithm comes to step 4 and sets C to a value $C_0 > L$; this can be only if $y \notin M$, because the algorithm ends just after having marked y . Moreover C_0 must be the minimum value of U on $\text{adj}(M)$, implying $L < U(z)$ for any $z \in \text{adj}(M)$.

By definition of L there exists an L -path $\gamma = (x_1 = x, \dots, x_n = y)$ joining x and y , that is $L \geq U(x_j)$ for each $j = 1, \dots, n$. The last two inequalities say that γ cannot intersect $\text{adj}(M)$. But this is absurd, since $x \in M$ and $y \notin M$. \square

The UTN program

Let S^1 denote the circle $\{z \in \mathbb{C} \text{ such that } |z| = 1\}$, and write \mathbb{Z}_k for the ring of integers modulo k . If the conformational space X is homeomorphic to an n -dimensional torus $S^1 \times \dots \times S^1$, then there is a natural and simple way to build a graph G which gives a good approximation of X .

By choosing a positive integer m_j for each circle, we consider the following (injective) map:

$$\varphi : ([a_1], \dots, [a_n]) \mapsto (\varphi_{m_1}(a_1), \dots, \varphi_{m_n}(a_n)) \in S^1 \times \dots \times S^1 \cong X$$

where

$$\varphi_m : [a] \in \mathbb{Z}_m \mapsto \exp\left(\frac{2\pi i a}{m}\right) \in S^1$$

We set $V := \mathbb{Z}_{m_1} \times \dots \times \mathbb{Z}_{m_n}$; φ identifies the vertices V of the graph with a “grid” $\varphi(V)$ of points on X . By composition with φ , we define the energy function U on V from the energy function on X .

Since the edges of G must correspond to “small” movements on the space X , we build E by putting in it all the pairs of vertices $\{(x_1, \dots, x_n), (y_1, \dots, y_n)\}$ such that

$$\max_j d_{m_j}(x_j, y_j) = 1$$

(here $d_k([a], [b]) = \min(|a - b|, k - |a - b|)$, the cyclic distance in \mathbb{Z}_k).

The UTN program, written in the C language, implements this case. The user has to supply a configuration file, containing the values for n, m_1, \dots, m_n , and a data file, with the samples of the various values of U . Some example data files, along with the source code of the software, are available.

Examples

To show how the program UTN works, we describe an analysis of the conformational behaviour of diphenylmethane, 1,2-diphenylethane and 1,2-diphenylpropane. We decided to present these compounds, here, because already there exist some conformational studies on these compounds which can be compared with our results (Barnes et al., 1981; Ivanov, Pojarlieff & Tyutyulkov, 1976; Jacobus, 1976; Eliel et al., 1965; Clark, 1985; Jeffrey, 1945; Cruickshank, 1949; Harada, Ogawa & Tomoda, 1995; Kahr et al., 1995).

The conformational space of each molecule was systematically searched by means of the Search_Compare[®] program, which is part of the molecular-modeling programs of MSI. Discover[®] was used to calculate the energy contents of each conformation, using the CVFF force field (Dauber-Osguthorpe et al., 1988). The images regarding the analysis of the results have been made with the Insight II[®] interface. The MSI suite runs on a IBM RISC 3AT computer.

Once we determined all the conformations, these were minimized keeping the torsion angles to their current values by means of a torsion force of $5 \cdot 10^4$ kcal mol⁻¹.

In the diphenylmethane case, each rotatable bond was scanned by using a ϕ -increment of 5° from 0° to 180°, this latter upper limit being chosen because of the intrinsic rotational symmetry of the phenyl ring. Thus 1296 structures were generated.

For the 1,2-diphenylethane, the angular increment was set to 5° for τ_1 and τ_3 and 10° for τ_2 , with angular amplitudes of 180°, 360° and 180° for τ_1 , τ_3 and τ_2 respectively. A total of 46656 conformations was produced.

Finally, 139968 conformations were originated from the systematic search on the 1,2-diphenylpropane by using steps of 10° for each scanned torsion and amplitudes set to 180°, 360°, 180° and 120° for $\omega_1, \omega_2, \omega_3$ and ω_4 respectively.

Results

Diphenylmethane

The UTN1 routine found out two isoenergetic minima in the bidimensional potential energy surface (see Figure 1). The energy barrier for the isomers' interconversion, as computed by UTN2, is ca. 2.5 kcal mol⁻¹, being the transition state characterised by an eclipsed disposition of the two phenyl rings.

Regarding the experimental evidences, we have found only one structure in the solid state for diphenylmethane (Barnes et al., 1981). The experimental torsion angles are

64° and 72° respectively for ϕ_1 and ϕ_2 . In our systematic conformational search the conformation having $\theta_1=65^\circ$ and $\theta_2=70^\circ$ is *ca.* 1 kcal mol⁻¹ higher than the absolute minimum conformation.

1,2-Diphenylethane

The UTN1 routine found three energy minima in the three-dimensional conformational space of the 1,2-diphenylethane molecule (see Figure 2), two of which show a \pm synclinal ($\pm 70^\circ$) arrangement of the central torsion angle, and the third one (the absolute minimum) a *trans* conformation of the central torsion τ_2 . Concerning the dihedral angles τ_1 and τ_3 , we have found that the three minima values lie in the range 85°-95°. All the retrieved X-ray data (Jeffrey, 1945; Cruickshank, 1949; Harada, Ogawa & Tomoda, 1995; Kahr et al., 1995) shown centrosymmetric molecular structures having antiperiplanar conformation ($\tau_2=180^\circ$) and \pm synclinal values for τ_1 and τ_3 (min. value $\pm 69^\circ$, max. value $\pm 73^\circ$).

Regarding theoretical calculations, some results have been already obtained; MM3 calculations (Harada, Ogawa & Tomoda, 1995) give for the torsion angles τ_1 and τ_3 values of $\pm 90^\circ$. About the central dihedral angle, some theoretical computations have been reported (Ivanov, Pojarlieff & Tyutyulkov, 1976, Jacobus, 1976) which state the synclinal conformation [$\tau_2 = \pm 60(\pm 30)^\circ$] (Klyne & Prelog, 1960) to be the preferred one, while the MM2 force field (Eliel et al., 1965; Clark, 1985) indicates the *anti* form to be the most stable. Our results indicate the synclinal conformers, relative to τ_2 value, to be ~ 0.3 kcal mol⁻¹ higher in energy than the antiperiplanar one, being the energy barrier for the isomers' interconversion of ~ 3.5 kcal mol⁻¹. Both the isoenergetic mirror-like transition states exhibit a \pm anticlinal conformation relatively to the central C_{al} - C_{al} bond.

1,2-Diphenylpropane

Four are the energy minima lying on the four-dimensional conformational space (see Figure 3). Three of them, having ω_2 of -70°(gauche1), +70°(gauche2) and +80°(gauche3), can be described as synclinal or *gauche* isomers, while the fourth has an antiperiplanar or *anti* conformation relatively to ω_2 (-170°). The gauche1 isomer resides in the absolute minimum separated by an energy barrier of ~ 4 kcal mol⁻¹ from the anti one, which is higher in energy of only 1.34 kcal mol⁻¹. The transition state is characterised by an -anticlinal conformation in respect to ω_2 . This result, which is in contrast with the intuitive idea that the steric interactions in a *gauche* conformer might be more relevant than those occurring in the corresponding *anti* one, was already pointed out in a theoretical study concerning the 1,2-diphenylpropane molecule (Jacobus, 1976). In this case, also, MM2 predicts (Eliel et al., 1965; Clark, 1985) the *anti* form as the most stable, accordingly to the results of an experimental solution study performed on the molecule (Jacobus, 1976).

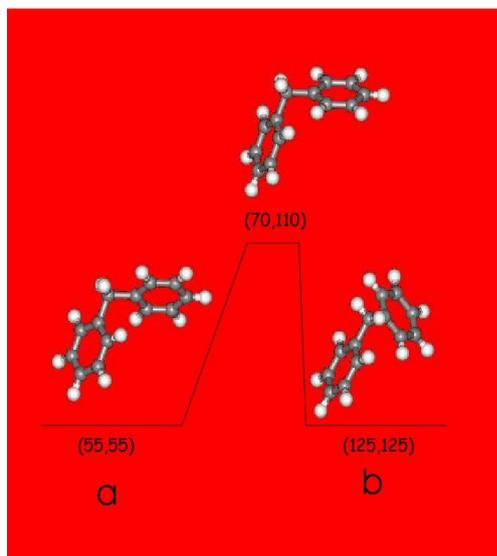


Figure 1: Conformation of the found minima and of the transition state of diphenylmethane

(click on the image to go back)

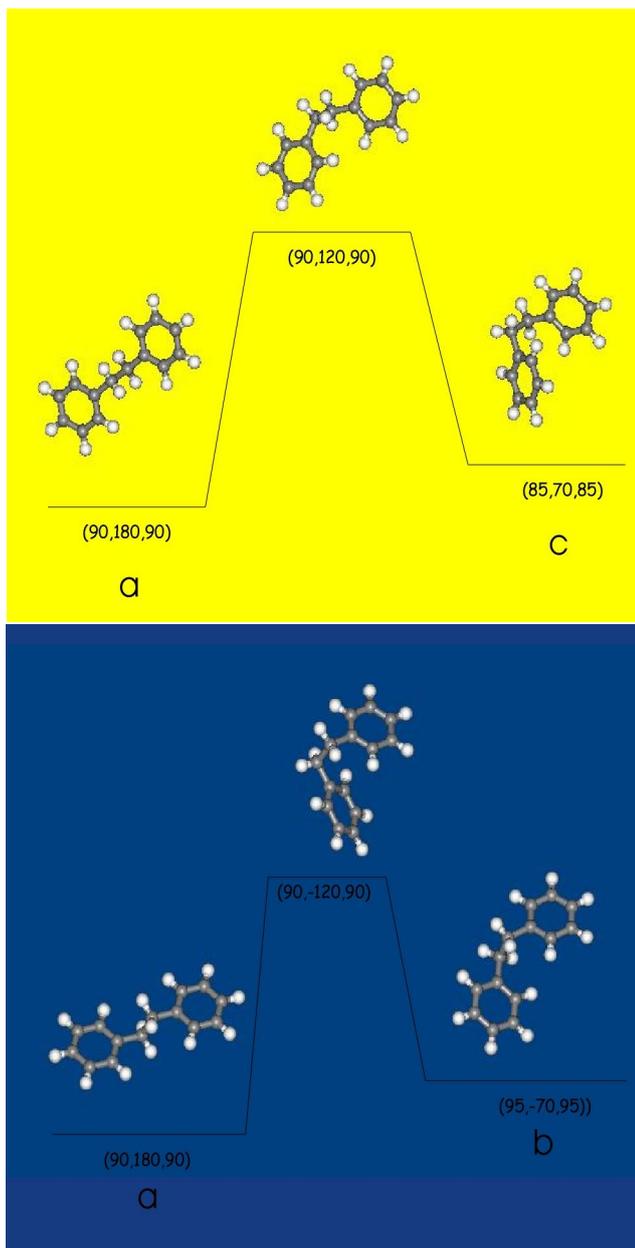


Figure 2: Conformation of the found minima and of the transition states of 1,2-diphenylethane

(click on any image to go back)

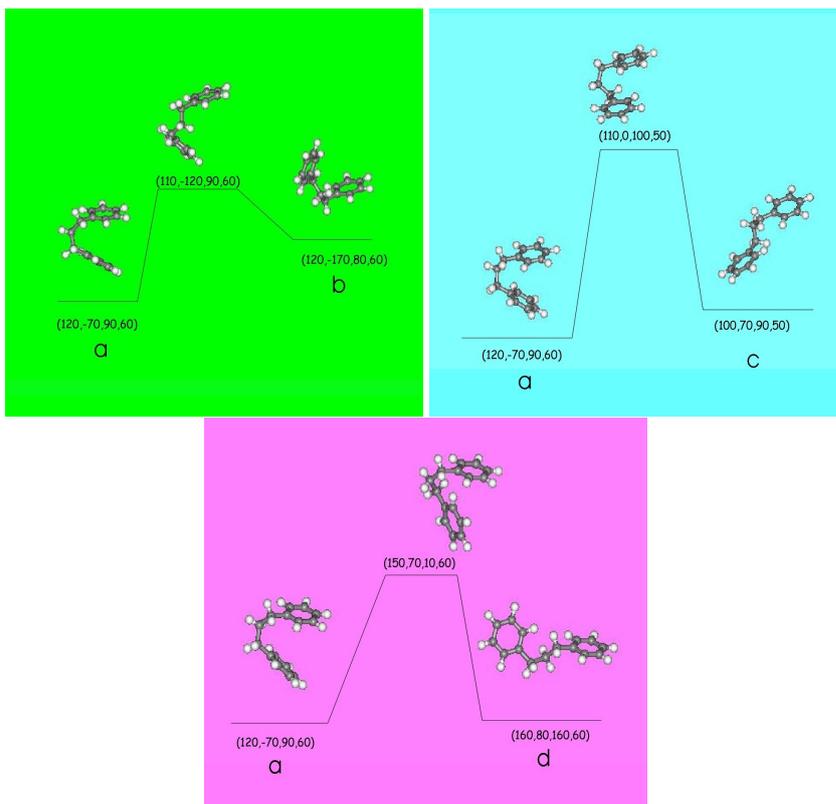


Figure 3: Conformation of the found minima and of the transition states of 1,2-diphenylpropane

(click on any image to go back)

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