Geometry Optimization and Conformational Analysis through Generalized Simulated Annealing

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Abstract

On statistical-mechanical grounds, a stochastic optimization technique (*Generalized Simulated Annealing*) has been recently proposed which contains both *Simulated Annealing* (Kirkpatrick et al 1983) and *Fast Simulated Annealing* (Szu 1986) as particular cases. This technique can be faster than both in detecting global (and also local) minima. Its utility in quantum chemistry is here illustrated, through the use of a semi-empirical quantum method, on molecules of the series CH_3-R (C_2H_6, CH_3COH, CH_3OH) , H_2X_2 (H_2O_2, H_2S_2), X_2Y_4 (N_2H_4, P_2H_4, N_2F_4) as well as for double bond (C_2H_4 and CH_2NH).

1 Introduction

It is well known that, in general, a molecular system can exist in different conformational geometries, which are tree-dimensional arrangements of atoms in a structure. The number of conformations increases with the molecule size. In particular, molecules of biological and farmacological interest present thousands of local minima (or conformations). The great difficulty, in this subject, is to find *global* minima and not to get trapped in one of the many *local* minima. This fact has led to the appearance of different theoretical methods, in quantum chemistry[1], to describe the molecular conformations as well as to obtain the optimized geometry.

In general, theoretical methods are based on the gradient descent approach. It is known that the gradient method indistinctly provides both global and local minima, consequently, to find the global minimum, the brute-force strategy has been the usual tool.

Recently, the so-called *simulated annealing methods* have demonstrated important successes in the description of a variety of global extremization problems. Simulated annealing methods have attracted significant attention as suitable for optimization problems of large scale, especially those where a desired global minimum is hidden among many local minima. The basic aspect of the simulated annealing method is its analogy with thermodynamics, especially with the way that liquids freeze and crystallize, or metals cool and anneal. The first nontrivial solution along this line was provided by Kirkpatrick et al [2, 3] for classical systems, and also extended by Ceperley and Alder [4] for quantum systems. It strictly follows the quasi-equilibrium Boltzmann-Gibbs statistics using a *Gaussian visiting distribution*, and is sometimes referred to as *Classical Simulated Annealing* (CSA) or *Boltzmann machine* . The next interesting step in this subject was Szu's proposal [5] to use a *Cauchy-Lorentz visiting distribution*, instead of a Gaussian one. This algorithm is referred to as the *Fast Simulated Annealing* (FSA) or *Cauchy machine.*

In recent years, some authors [6, 7] have applied the Boltzmann machine to describe molecular conformations and the associated global minima.

On the other hand, it has been recently proposed [8] a *Generalized Simulated Annealing* (GSA) approach which closely follows the recently Generalized Statistical Mechanics [9, 10]; it contains both Boltzmann and Cauchy machines as particular cases, with the supplementary bonus of providing an algorithm which is *even quicker* than that of Szu.

We propose in this work the use of this generalized algorithm in order to describe molecular conformations and to optimize the molecular geometry. To illustrate this, we make a coupling between a semi-empirical quantum program (MOPAC-package) [11] and the GSA routine.

In section 2, we discuss the algorithm used for recovering the global minima. In section 3, we present results concerning a variety of molecular structures. We conclude in section 4.

2   Generalized Simulated Annealing in Quantum Chemistry

Here, we implement the GSA algorithm on a semi-empirical quantum method to calculate the minimal energy conformational geometry for different molecular structures.This technique can be indifferently applied on all "ab-initio " or semi-empirical quantum methods. We have used, in present case, a semi-empirical one only for computational convenience.

The GSA method is based on the correlation between the minimization of a cost function (total electronic energy) and the geometries randomly obtained through a slow cooling. In this technique, an artificial temperature is introduced and gradually cooled, in complete analogy with the well known annealing technique frequently used in metallurgy when a molten metal reaches its crystalline state (global minimum of the thermodynamical energy). In our case the temperature is intended as an external noise.

The procedure consists in comparing the total semi-empirical energies for two random geometries obtained from the GSA routine. The artificial temperature (or set of temperatures) acts as a source of stochasticity extremely convenient for eventually detrapping from local minima. Near the end of the process, the system hopefully is inside of the attractive basin of the global minimum (or in one of global minima, if there is degeneracy). The challenge is to get cool the temperature the quickest we can but still having the guarantee that no irreversible trapping at any local minimum occurs. More precisely speaking, we search for the quickest annealing (that is, in a some sense approaching a quenching) which preserves the probability of ending in a global minimum being equal one.

The present GSA routine was built using the same procedure presented in [8]. We apply this algorithm in order to study a set of molecules which present one or more different conformations by rotating a particular dihedral angle (θ) around the X-Y bonds, i.e., in this case we have only *one* degree of freedom ($D = 1$) . In summary the whole algorithm for mapping the global minimum of the energy function is:

(i) Fix the parameters (q_A, q_V) (we recall that (q_A, q_V) = (1, 1) and (1, 2) respectively correspond to the Boltzmann and Cauchy machines). Start, at $t = 1$, with an arbitrary value θ_1 and a high enough value $T_{q_V}(1)$ (*visiting temperature*) and cool as follows:

$$T_{q_V}^V(t) = T_{q_V}(1)\frac{2^{q_V-1} - 1}{(1 + t)^{q_V-1} - 1} \qquad (1)$$

where t is the discrete time corresponding to the computer iteration, and q_A (q_V) is the *acceptance index* (*visiting index*).

(ii) Then randomly generate θ_{t+1} from θ_t by using the *visiting distribution probability* g_{qv} as

$$g_{qv}(\Delta\theta_t) = \left(\frac{qv-1}{\pi}\right)\frac{\Gamma\left(\frac{1}{qv-1}+\frac{D-1}{2}\right)}{\Gamma\left(\frac{1}{qv-1}-\frac{1}{2}\right)}\frac{\left[T_{qv}^V(t)\right]^{-\frac{D}{3-qv}}}{\left\{1+(qv-1)\frac{(\Delta\theta_t)^2}{\left[T_{qv}^V(t)\right]^{-\frac{2}{3-qv}}}\right\}^{\frac{1}{qv-1}+\frac{D-1}{2}}} \tag{2}$$

with $-180 < \Delta\theta < 180$; Γ is the gamma function. This procedure assures that the system can both escape from any local minimum and explore the entire energy surface.

(iii) Then calculate the total electronic energy $E(\theta_{t+1})$ by using the MOPAC program:

If $E(\theta_{t+1}) < E(\theta_t)$, replace θ_t by θ_{t+1};
If $E(\theta_{t+1}) > E(\theta_t)$, run a random number $r \in [0,1]$: if $r > P_{q_A}$ (*acceptance probability*) given by

$$P_{q_A}(\theta_t \rightarrow \theta_{t+1}) = \frac{1}{1+\left\{1+(q_A-1)[E(\theta_{t+1})-E(\theta_t)]/T_{q_A}^A(t)\right\}^{\frac{1}{q_A-1}}} \tag{3}$$

with $(T_{q_A}^A(t) = T_{qv}^V(t))$, retain θ_t ; otherwise, replace θ_t by θ_{t+1}.

(iv) Calculate the new temperature T_{qv}^V using Eq.(1) and go back to (ii) until the minimum of $E(\theta)$ is reached within the desired precision.

In short, this computational method is based on a stochastic dynamics which enables, with probability one, the identification of a global minimum of the electronic energy hiper-surface, which depends on a continuous D-dimensional variable $\vec{x}$, (in this paper $D = 1$ and $x = \theta$ is the dihedral angle). While the number t of computational iterations increases, it might happen that θ_t provisorily stabilizes on a given value, and eventually abandons it running towards the global minimum. This temporary residence can be used, as a bonus of the present method, to identify some of the local minima. The ordinate (*Number of cycles*), in the figures 1 to 4, represents the frequency (temporary residence) of the positive trials when a tested angle appears.

In figures 1 to 4 we observe the arising of some dihedral angles (noises) which do not represent the searched local or global minima. They appear with minor frequency, and in order to eliminate this noises it is convenient to repeat the procedure (*i*) to (*iv*) using different initial conditions. In this case we can also verify that all degenerate minima will be visited with the same frequency.

3 Applications

We have applied the MOPAC-GSA approach to find the possible conformations of some important molecular systems. We have also treated the barriers associated with rotations around double bonds.

The different minima were obtained by considering the group G fixed and rotating the group R around the binding $G - R$ axis, as a rigid rotor. Here, all bond lengths and all other angles are held fixed during the rotation, and are assigned standard or experimental values. We have used, for simplicity, the (1,2) machine. If quicker convergence is required, the (1,2.9) machine can be more appropriate (see [8]).

We recall that MOPAC is a quantum chemistry program package, which contains a variety of semi-empirical approximations (Hamiltonians). In this paper, to calculate the electronic energy, we have used the semi-empirical MNDO-PM3 Hamiltonian [12].

Series CH$_3$-R

Within the series CH$_3$- (Radical) we have studied the compounds CH$_3$-CH$_3$ (ethane), CH$_3$-COH (acethaldehyde) and CH$_3$-OH (methyl alcohol). As shown in Figures 1a-c our method predicts, for all compounds, the eclipsed conformation as being the global minimum. The results obtained using the MOPAC-GSA approach agree with the results obtained from pure MOPAC calculations. In this case the fixed group G is the CH$_3$ one.

Fig. 1a-c

Series HX-R

In case of the HO$-$OH (hydrogen peroxide) and HS$-$SH (hydrogen persulphide) the eclipsed geometry corresponds to the equilibrium conformation, which is in relative agreement with the expected results from the semi-empirical method. In both cases we have fixed the group HX and rotated the radical R around the bond HX-R. See Figures 2a-b.

Fig. 2a-b

Series X_2Y_4

In this series, we have analyzed the compounds N_2H_4 (hydrazine), P_2H_4 (diphosphine) and N_2F_4 (tetrafluorohydrazine). Our method, as well the pure MOPAC ones, predict that the most stable conformation for both molecules is the eclipsed geometry. In all cases we have fixed the group X_2Y and rotated the R one. See Figures 3a-c.

Fig. 3a-c

Double Bond

Another interest in this direction is the study of the barriers to rotation about a double bond. The examined compounds are the CH_2-CH_2 (ethylene) and CH_2-NH (methyleneimine), which have the *cis* and *trans* as the most stable conformations. We have rotated around the $CH_2 - R$. See Figures 4a-b.

Fig. 4a-b

4 Concluding Remarks

We conclude from these preliminary studies that the MOPAC-GSA approach is a good qualitative and quantitative indicator of conformational molecular preference. We would like to emphasize that the GSA , differently from the gradient descent approach, enables us to map out local minima while the global minimum is searched.

We intend that this technique can be indifferently applied on all "ab-initio" or semi-empirical quantum methods, since the GSA routine makes no interference in the quantum calculus. In particular, we have used the semi-empirical MNDO-PM3 approximation, only for computational convenience.

The GSA method converges faster when the parameter q_V increases and has both the *Classical Simulated Annealing* (CSA) and the *Fast Simulated Annealing* (FSA) as particular cases. In this paper we have used $q_V = 2$ (Cauchy machine or FSA) and $D = 1$, and have applied the algorithm in order to study a set of molecules which present one or more different conformations by rotating a particular dihedral angle (θ) around the X-Y bonds. This procedure can be straightforwardly extended to any dimension $D > 1$.

Caption for Figures

Fig. 1- Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) C_2H_6 (ethane), (b) CH_3COH (acethaldehyde) and (c) CH_3OH (methyl alcohol).

Fig. 2- Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) H_2O_2 (hydrogen peroxide) and (b) H_2S_2 (hydrogen persulphide).

Fig. 3- Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) N_2H_4 (hydrazine), (b) P_2H_4 (diphosphine) and (c) N_2F_4 (tetrafluorohydrazine).

Fig. 4- Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) C_2H_4 (ethylene) and (b) CH_2NH (methyleneimine).
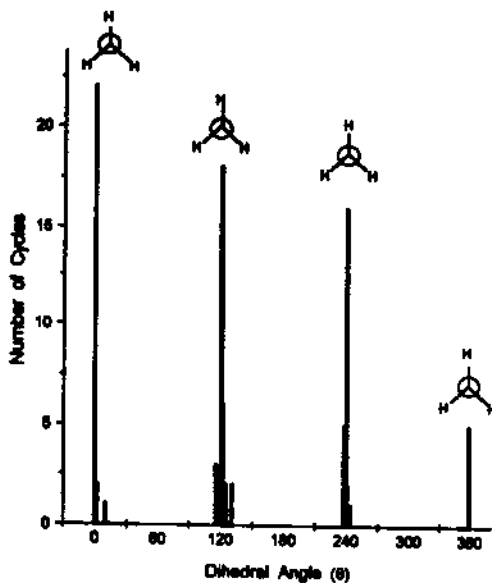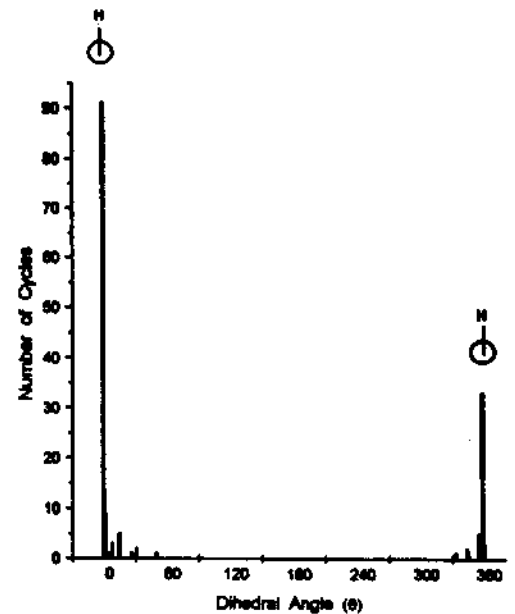
Fig. 1a
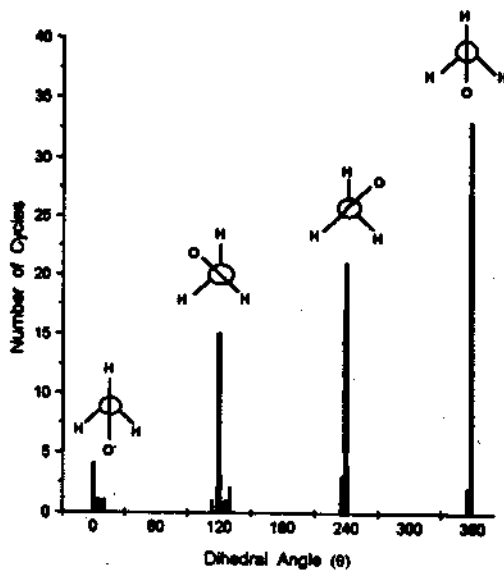
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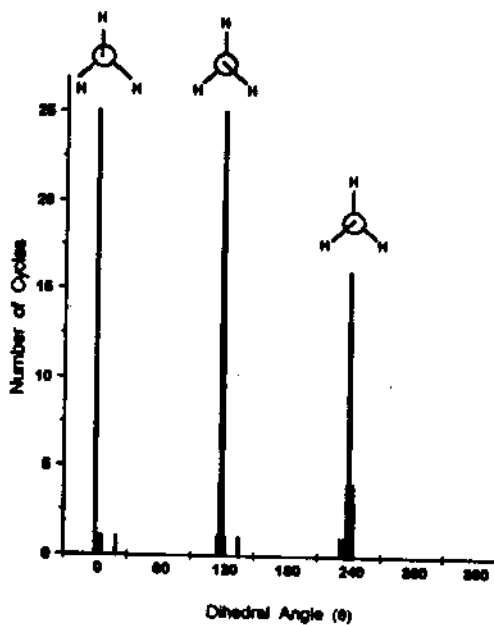
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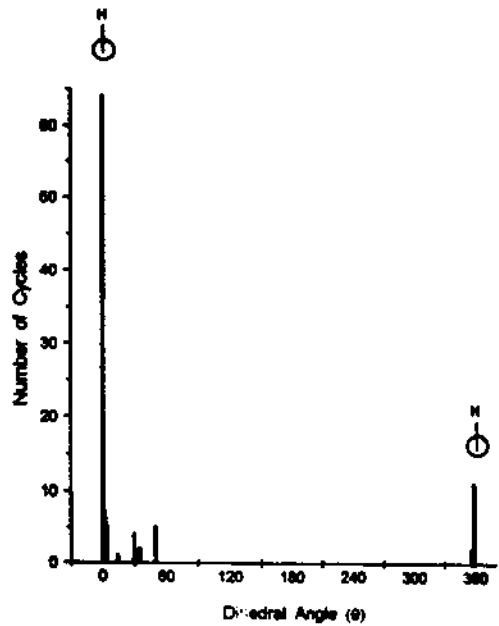
Fig. 2a

Fig. 2b

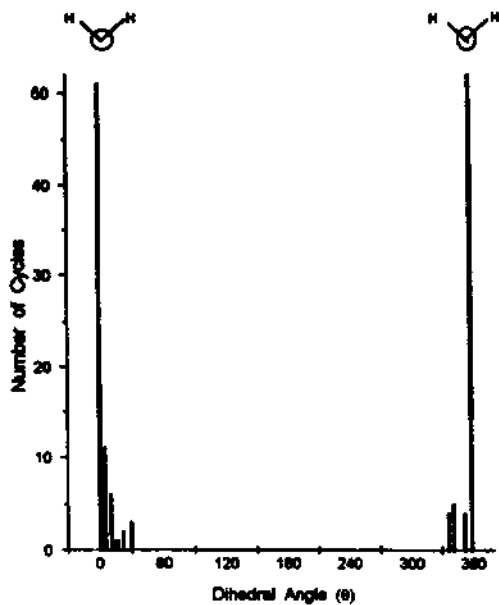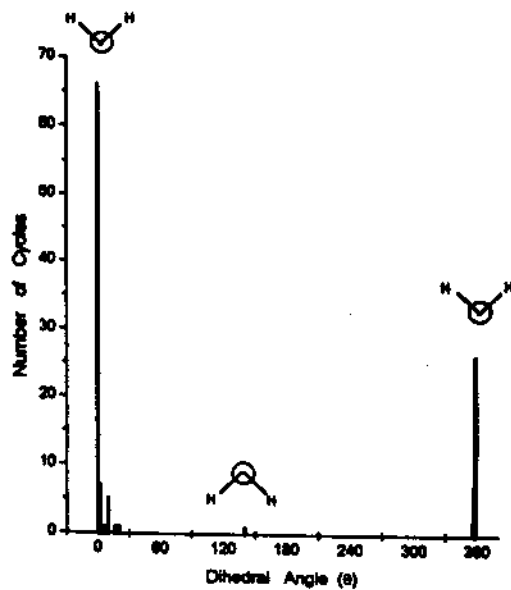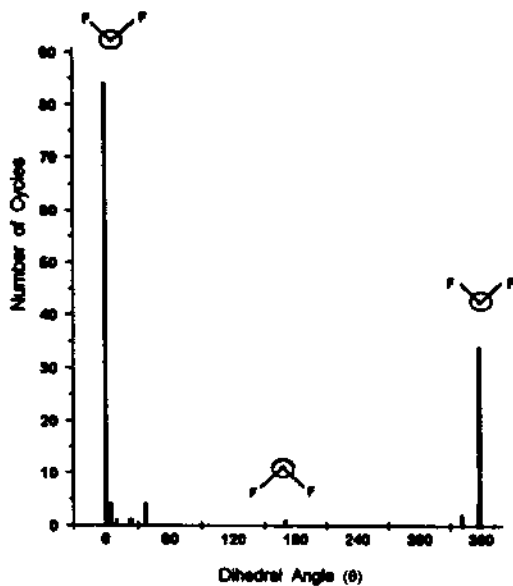Fig. 3a

Fig. 3b

Fig. 3c
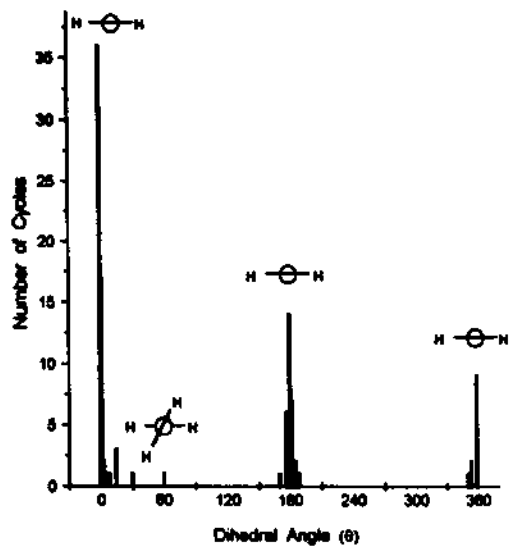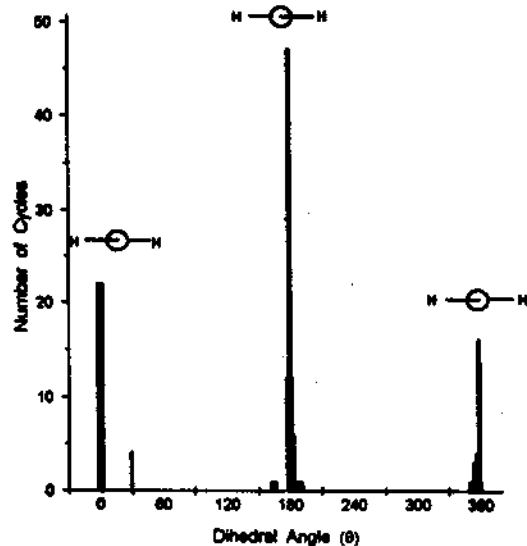
Fig. 4a

Fig. 4b

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