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 classical 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 semiempirical 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), for double bonds (C_2H_4 and CH_2NH), and finally for H_2O_3.

Introduction

It is well known that, in general, a molecular system can exist in different conformational geometries, which are three-dimensional arrangements of atoms in a structure. The number of conformations increases with the molecule size. In particular, molecules of biological and pharmacological 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.

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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 discussion 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 Ceperely 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 and Hartley'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, what has been recently proposed [8] is a *generalized simulated annealing* (GSA) approach which closely follows the recently generalized thermostatistics [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 and Hartley. Recently, this method has been applied with success in different subjects: genetics [11], the traveling salesman problem [12], and fitting curves by simulated annealing [13].

We propose in this work the use of this generalized algorithm to describe molecular conformations and to optimize the molecular geometry. To illustrate this, we make a coupling between a semiempirical quantum program (MOPAC package) [14] and the GSA routine.

In the next section, we discuss the algorithm used for recovering the global minima. Then, we present results concerning a variety of molecular structures followed by conclusions.

Generalized Simulated Annealing in Quantum Chemistry

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

The GSA method is based on the correlation between the minimization of a cost function (molecular 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 semiempirical 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 the global minima if there is degeneracy). The challenge is to lower the temperature the quickest we can but still have the guarantee that no irreversible trapping at any local minimum occurs. More precisely, we search for the quickest annealing (i.e., in some sense approaching a quenching) which preserves the probability of ending in a global minimum of 1.

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 dihedral angles ($\boldsymbol{\theta}$) around the X–Y bonds. In summary the whole algorithm for mapping the global minimum of the energy function is as follows:

(i) Fix the parameters (q_A, q_V) (we recall that (q_A, q_V) values of $(1, 1)$ and $(1, 2)$ correspond to the Boltzmann and Cauchy machines, respectively). Start, at $t = 1$, with

an arbitrary value $\boldsymbol{\theta}_1$ and a high enough value $T_{q_V}(1)$ (*visiting temperature*) and cool as follows:

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

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 $\boldsymbol{\theta}_{t+1}$ from $\boldsymbol{\theta}_t$ by using the *visiting distribution probability* g_{q_V} as

$$g_{q_V}(\Delta\theta_t) = \left(\frac{q_V-1}{\pi}\right)^{D/2}\frac{\Gamma[1/(q_V-1)+(D-1)/2]}{\Gamma[1/(q_V-1)-1/2]} \times \frac{\left[T_{q_V}^V(t)\right]^{-D/(3-q_V)}}{\left\{1+(q_V-1)\dfrac{(\Delta\theta_t)^2}{\left[T_{q_V}^V(t)\right]^{-2/(3-q_V)}}\right\}^{1/(q_V-1)+(D-1)/2}} \quad (2)$$

with $-180 < \Delta\theta < 180$; Γ is the gamma function; D is the number of components of $\boldsymbol{\theta}$. 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 $E(\boldsymbol{\theta}_{t+1})$ by using the MOPAC program:

If $E(\boldsymbol{\theta}_{t+1}) < E(\boldsymbol{\theta}_t)$, replace $\boldsymbol{\theta}_t$ by $\boldsymbol{\theta}_{t+1}$.

If $E(\boldsymbol{\theta}_{t+1}) > E(\boldsymbol{\theta}_t)$, run a random number $r \in [0, 1]$: if $r < P_{q_A}$ (*acceptance probability*) given by

$$P_{q_A}(\boldsymbol{\theta}_t \rightarrow \boldsymbol{\theta}_{t+1}) = \frac{1}{1+\{1+(q_A-1)[E(\boldsymbol{\theta}_{t+1})-E(\boldsymbol{\theta}_t)]/T_{q_A}^A(t)\}^{1/(q_A-1)}} \quad (3)$$

with $T_{q_A}^A(t) = T_{q_V}^V(t)$, retain $\boldsymbol{\theta}_t$; otherwise, replace $\boldsymbol{\theta}_t$ by $\boldsymbol{\theta}_{t+1}$.

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

In short, this computational method is based on a stochastic dynamics which enables, hopefully with probability 1, the identification of a global minimum of the energy hypersurface, which depends on a continuous D-dimensional variable $\boldsymbol{\theta}$ [in this article $\boldsymbol{\theta} = (\theta_1, \theta_2)$ are dihedral angles]. While the number t of computational iterations increases, it might happen that $\boldsymbol{\theta}_t$ provisorily stabilizes on a given value and eventually abandons it running toward 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 Figures 1–4 represents the frequency (temporary residence) of the positive trials when a tested angle appears.

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

In Figure 6 we present the result obtained for the molecule H_2O_3 (Fig. 5) with two parameters to be optimized ($D = 2$), i.e., $\boldsymbol{\theta} = (\theta_1, \theta_2)$.

Applications

We have applied the MOPAC–GSA approach with $(q_V, q_A) = (2, 1)$ 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 semiempirical approximations (Hamiltonians). In

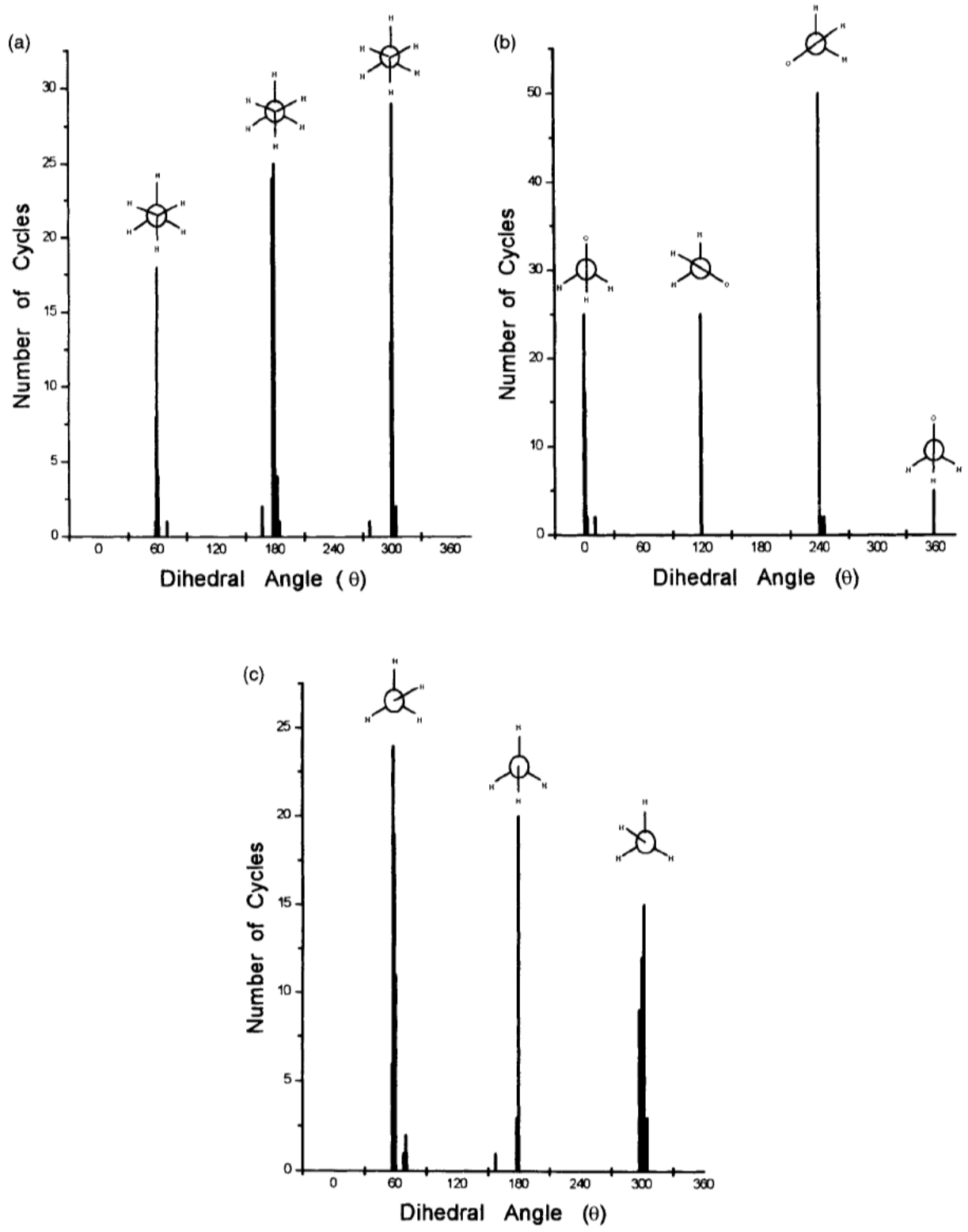

FIGURE 1. Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) C_2H_6 (ethane), (b) CH_3COH (acetaldehyde), and (c) CH_3OH (methyl alcohol).

this article, to calculate the energy (heat of formation), we have used the semiempirical MNDO-PM3 Hamiltonian [15].

CASE ONE-DIMENSIONAL ($D = 1$)

Series CH_3–R

Within the series CH_3–R we have studied the compounds CH_3–CH_3 (ethane), CH_3–COH (acethaldehyde), and CH_3–OH (methyl alcohol). As shown in Figures 1(a)–(c) our method predicts, for all compounds, the eclipsed conformations 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.

Series HX–R

In the case of the HO–OH (hydrogen peroxide) and HS–SH (hydrogen persulfide) the eclipsed geometry corresponds to the equilibrium conformation, which is in acceptable agreement with the expected results from the semiempirical method. In both cases we have fixed the group HX and rotated the radical R around the bond HX–R. See Figures 2(a) and (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 as 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 3(a)–(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 cis and trans as the most stable conformations. We have rotated around the CH_2–R. See Figures 4(a) and (b).

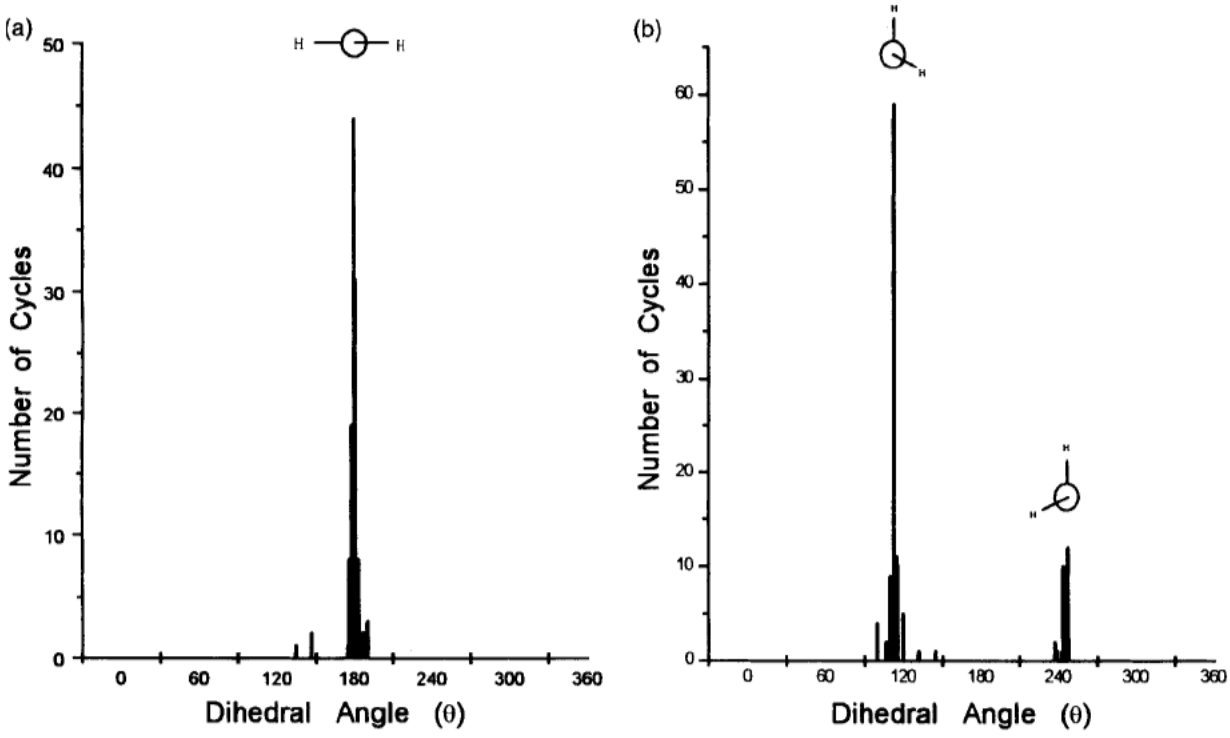

FIGURE 2. Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) H_2O_2 (hydrogen peroxide) and (b) H_2S_2 (hydrogen persulfide).

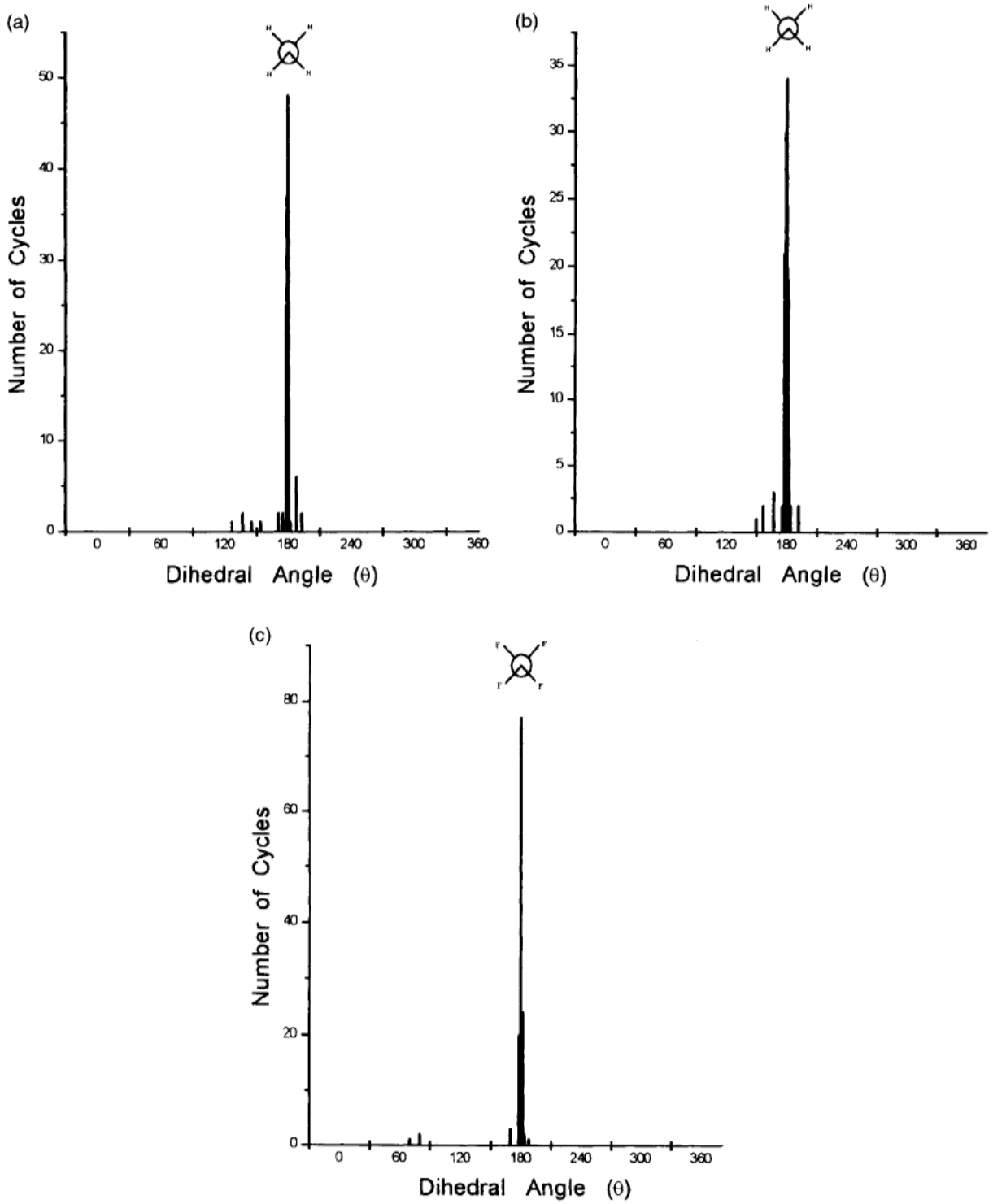

FIGURE 3. Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) N_2H_4 (hydrazine), (b) P_2H_4 (diphosphine), and (c) N_2F_4 (tetrafluorohydrazine).

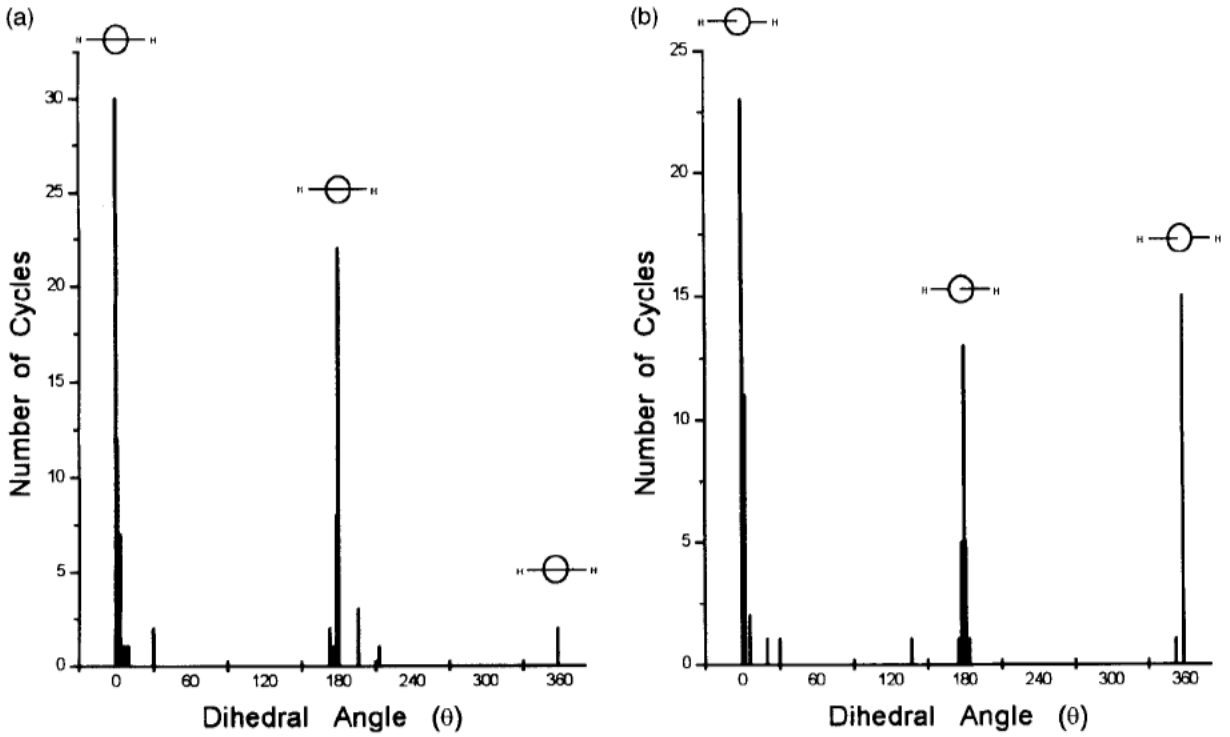

FIGURE 4. Profile associated with the possible equilibrium (global minima) conformational geometries of the molecular structures: (a) C_2H_4 (ethylene) and (b) CH_2NH (methyleneimine).

CASE TWO-DIMENSIONAL ($D = 2$)

As an illustration of the $D = 2$ case, we have applied the above presented algorithm to map the energy surface associated with the molecule H_2O_3 (Fig. 5) in terms of (θ_1, θ_2). In this case, we have rotated, stochastically, the θ_1 and θ_2 angles to calculate the molecular energy using the MNDO-PM3 Hamiltonian. As shown in Figures 6(a) and (b), for the compound H_2O_3, the skew conformation $(\theta_1, \theta_2) \simeq (68°, 68°)$ has been found as the most stable.

To obtain the complete mapping of the energy hypersurface, in this simple case (H_2O_3), it is necessary to calculate the energy for each pair of angles (θ_1, θ_2) varying it in the range $[0, 360°]$. This method is computationaly expensive.

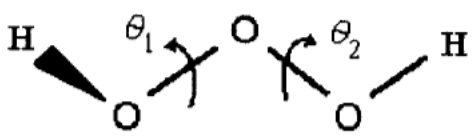

FIGURE 5. Molecule H_2O_3.

Using the present simulated annealing, we have obtained a good representative mapping of the energy, as shown in Figure 6, with 320 iterative cycles only.

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

The GSA method converges faster when the parameter q_V increases and has both the CSA and the FSA as particular cases. In this article we have used

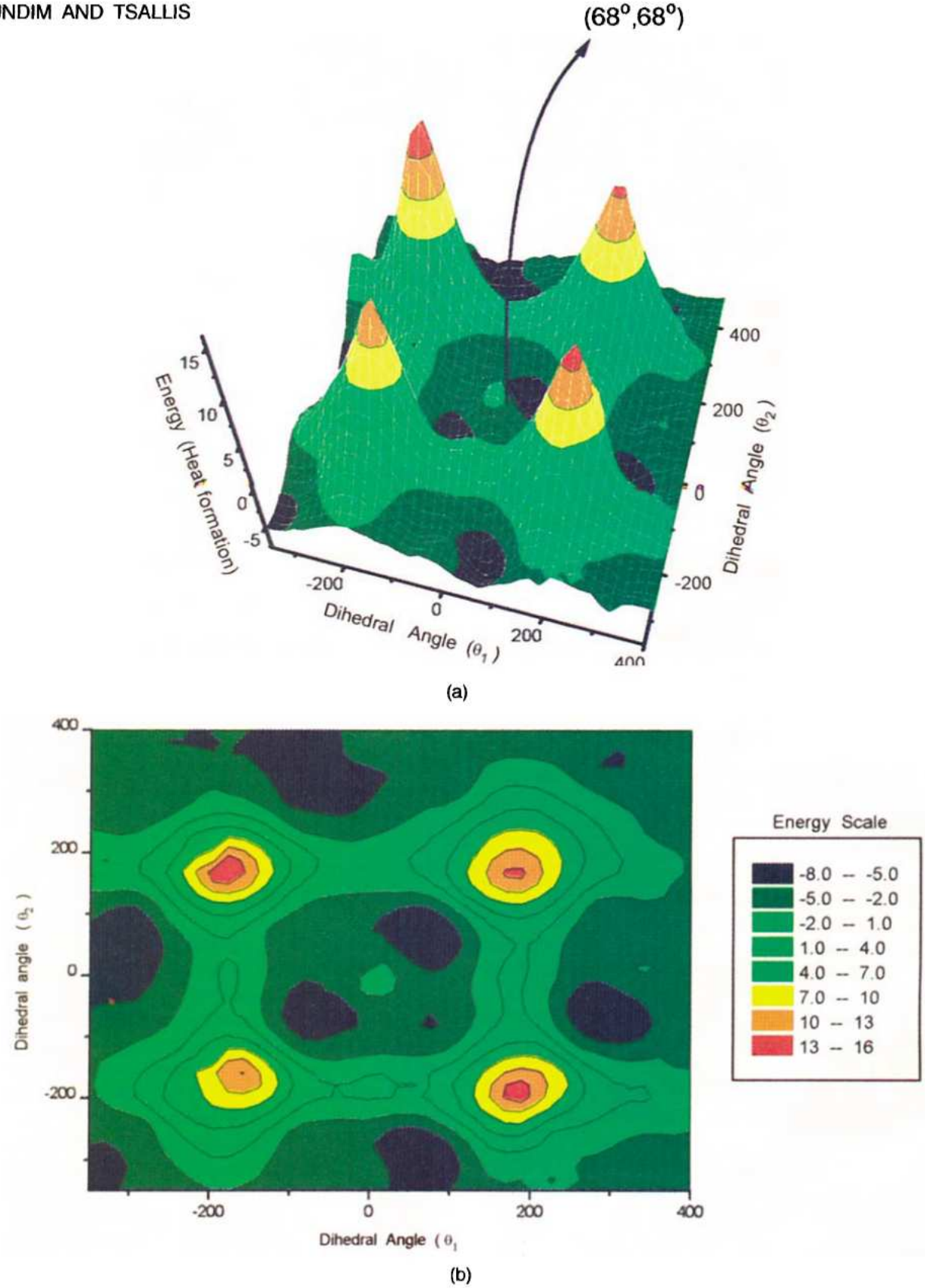

FIGURE 6. $D = 2$ case. Mapping of the molecular energy hypersurface for the compound H_2O_3. The energy function (formation heat) is expressed in kilocalories per moles and the angles θ_i in degrees. (a) Energy mapping is plotted through a three-dimensional surface; and (b) top view of (a).

$(q_V, q_A) = (2, 1)$ (Cauchy machine or FSA) for both the $D = 1$ and $D = 2$ cases. We have applied the algorithm to study a set of molecules which present one or more different equilibrium conformations by rotating a particular dihedral angle (θ) around the X–Y bonds. This procedure can be straightforwardly extended to any dimension $D > 2$.

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