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Conformational Analysis of Flexible Molecules: Location of the Global Minimum Energy Conformation by the Simulated Annealing Method

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Summary: A new computational method for the location of the lowest energy conformation of flexible molecules is reported. The technique, called simulated annealing, is discussed and several applications are described.

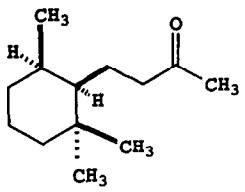
The study of the structure and chemistry of flexible organic molecules is a challenging problem of current interest. Most chemists accept the fact that the exact conformations of flexible molecules can not really be described quantitatively. The primary problem comes down to finding the lowest energy conformations among a large number of possible minimum energy structures. The "global-minimum problem" i.e. finding the lowest energy state overall, as opposed to a local minimum, has been an unsolved problem. Molecular mechanics energy calculations,[1] which nowadays are routine, are not usually done on all possible starting geometries and thus do not yield information on whether a particular conformation is actually the lowest energy one.

In order to find the global minimum, a "brute-force" strategy is generally employed. This method attempts to locate the global energy minimum by generation of a very large number of starting geometries, minimizing them to the nearest local minima, then throwing away the duplicates. As the number of starting geometries increases, this method should find the lowest conformation since all parts of the conformational space are sampled. This method is the basis for the "multiconformer" option in Still's program Macromodel[2], the "chain-buildup" procedure of Scheraga[3], or "Calc/Conf" from Chem-X.[4]

We describe here a new approach: a computer program that locates the global minimum energy conformation by searching conformation space using a Monte Carlo[5] approach known as simulated annealing.[6] This strategy[7] makes use of both energy and temperature. At a given temperature, the Metropolis algorithm is used to simulate the conformational equilibrium at that temperature. A sequence of decreasing temperatures is then employed to make use of the temperature dependency of the Boltzmann distribution. Because this approach simulates a real molecular system closely, it is not surprising that is more efficient in finding the global minimum. The program slowly lowers the

temperature until certain conformations are frozen out. Eventually, the temperature is low enough that the molecule is trapped in an energy well. If the "cooling schedule" is appropriate, the molecule should be trapped in the global energy minimum conformation.

For example, the relatively simple molecule cis-tetrahydroionone 1,



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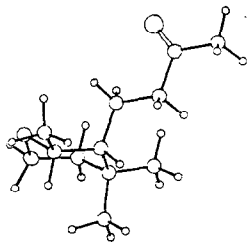


Figure 1. Global Minimum for cis-Tetrahydroionone (MM2 Energy = 75.84 Kjoul/mol)

is conformationally quite complex. While the six-membered ring is constrained to the chair form with the side-chain in an axial position, the three dihedral angles of the side chain leads to a large number of local minima. (In general, there are approximately three minima for each dihedral angle or in this case 3^3 = 27 *possible* minima.) In order to find these, the multiconformer option of Macromodel was used starting at a 30^o dihedral resolution (i.e. 576 starting geometries). Direct minimization of these 576 structures leads to 8 unique local minima within 20 Kjoul/mmol (cputime = 5 hours).[8] Using our simulated annealing program, with the MM2 force field and appropriate cooling, the global energy minimum (Figure 1) is found directly (cputime = 10 min.).

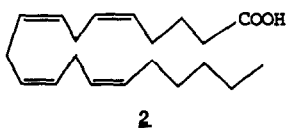
The simulated annealing process differs from a conventional iterative minimization process, i.e., the Newton-Raphson method, in that simulated annealing need not get stuck in local minima since transitions out of local minimum are always possible at nonzero temperatures. The Metropolis algorithm is used to provide an efficient simulation of the distribution of the conformers in equilibrium at a given temperature. In each step of the algorithm, a rotatable bond is selected randomly to be rotated a random number of degrees (ranging from -90 to 90 degrees) and the resulting change in energy of the molecule, ΔE is calculated according to the selected force field (MM2 for organic molecules or AMBER for peptides). If $\Delta E \leq 0$, the rotation is accepted, and the new conformation is used as the starting point for the next step. The case when $\Delta E > 0$ is treated probabilistically: the probability that the conformation is accepted is $P(\Delta E) = \exp(-\Delta E/kT)$. By repeating this basic step many times, the program simulates the thermal motion of the molecule in thermal contact with a heat bath at temperature T.[9]

The acceptance rate is optimized so that the annealing process will go primarily in the direction of decreasing energy, but enough uphill steps are carried out to make transitions out of local minima possible. The acceptance

rate of the basic steps in the Metropolis algorithm at each temperature is calculated, and at the beginning of Metropolis process at each new temperature, the step size of the random walk (the degree range of the rotation) is adjusted according to the acceptance rate of the Metropolis process at the last higher temperature.

In the whole annealing process, the lowest energy conformation found so far is kept a structure array and is updated whenever a lower one is found. At the end of the annealing process, the lowest energy conformation is optimized locally by a direct minimization procedure (block-diagonal Newton-Raphson).

Simulated annealing using our **Anneal-Conformer** program has been very successful in finding the global minimum for systems where the minimum is known. It also seems to find quite reasonable low energy minima for much more complex systems out of reach of "brute-force" techniques. For example, arachidonic acid[9] 2 is a very flexible molecule with 15 rotatable bonds (dihedral angles).



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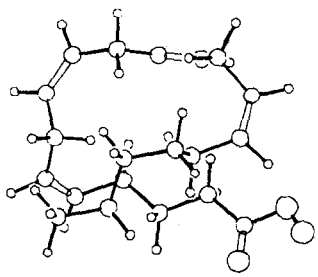

Figure 2: Arachidonic Acid
(MM2 Energy = -14.23 Kjoul/mol)

Given the assumption that there will be 3 minima for each dihedral angle this yields 3^{15} = 14,348,907 possible minima. This number is far beyond the capability of direct energy minimization. Simulated annealing gives the conformation shown in figure 2.

A second example is Met-enkephalin[10,11] (Tyr-Gly-Gly-Phe-Met) with 18 dihedral angles. Figure 3 shows the results of our **Anneal-Conformer** run on

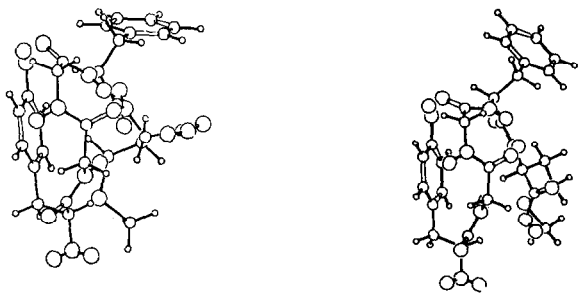

Figure 3: "Global Minima" of Met-enkephalin by Scheraga (-212.52)[11b] and this work (-221.91). Energies are in Kjoul/mol and were calculated using Amber.

this peptide using the completely extended geometry as a starting point. Our global minimum is lower in energy than that reported by Scheraga, although it should be pointed out that Scheraga used the ECEPP[12] force field whereas we used Amber.[13]

Finally extensive testing of the **Anneal-Conformer**[14,15] program with all twenty amino acids and with peptides up to $(Ala)_{10}$ leads us to the conclusion that the program is a powerful tool for searching for the global minimum energy conformations of flexible molecules. The program is also very efficient in terms of computer time. The global minimum of Met-enkephalin above was found in 20 minutes on our Vax 8600. Since often the problem is only picking reasonable low energy conformer, we believe the simulated annealing approach will become the method of choice.

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8. The minima are: 75.84, 77.75, 78.49, 79.60, 80.13, 80.68, 80.78 Kjoul/mol.
9. Typically 250 steps at a sequence of 50 different "temperatures" are used. Details of the cooling schedule are given in reference 7. Because of the random nature of the search, the global minimum is not found 100% of the time. For compound **1** (Figure 1), 17 different starting geometries were run a total of 73 times and the global minimum was found 68 times.
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15. A Vax version of **Anneal-Conformer** as well as instructions and test data is available on a Macintosh floppy (to be downloaded to a Vax with Kermit) or via Bitnet by sending $20 to the authors at the above address.

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