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Simulated Annealing of Rings using an Exact Ring Closure Algorithm

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Abstract

The method of simulated annealing has been combined with an exact ring closure algorithm to locate the global minimum of hydrocarbon rings without energy minimization. A new program called **ANNEAL-RING** carries out simulated annealing by computation of the exact new positions of three or more atoms and then application of the Metropolis Monte Carlo accept-reject criterion [$\exp(-\Delta E/RT)$] with cooling. Cyclononane, cyclodecane, cycloundecane and cycloheptadecane were studied.

Introduction

Despite advances in theory, almost all calculations are starting geometry dependent. A prerequisite for good results is a selection of "good" structures on which to base the calculations. Hence, a major question that always arises is the choice of starting geometries.[1] In conformational analysis for example, a judicious choice of starting geometries is necessary, and thus a set of good geometries is needed *a priori* to calculate a set of good geometries. This has led Allinger[2] to say: "results .... depend not so much on the force field being used, but on the intuition of the person doing the calculations, and on which starting geometries were used for the energy minimization." This intuition dependence of conformational analysis arises from the fact that many local minima exist on the potential energy surface. Typically, this surface is studied by deforming, then energy minimizing a structure. Since energy minimization drops the structure into the nearest well, it is easy to understand why analysis of a flexible molecule such as enkephalin, which is estimated to possess at least 10^{11} minima, requires prior structural insights.

The method of simulated annealing, originally developed by Kirkpatrick for computer circuit design,[3] has been employed in a wide variety of multivariate optimization problems.[4] Our group has recently extended simulated annealing to acyclic conformational analysis.[5] Other related studies have since appeared.[6] Simulated annealing is the Metropolis Monte Carlo[7] sampling of conformation space with gradual temperature reduction. By incrementally lowering the temperature, the available conformation space is gradually decreased until the molecule theoretically "freezes" into the global or one of the low energy minima. Like any Monte Carlo procedure, the success of simulated annealing depends upon sufficiently sampling the space.[8] To insure that a simulated annealing run has access to the entire conformation space, the run is started at a temperature high enough to allow the molecule to jump over any energy barrier. Therefore, whatever starting geometry is used, the molecule is immediately knocked into a random high energy state. Thus, simulated annealing is independent of the starting geometry.[9]

Conformational Analysis of Flexible Rings.

Deforming an *acyclic* flexible structure using simulated annealing simply requires randomly rotating any randomly chosen flexible dihedral angle. Unique new complexities are added when searching for conformations of flexible cyclic structures.[10] Rotating a dihedral in a *cyclic* structure will inevitably distort some of the bond lengths and bond angles of the molecule (figure 1a).

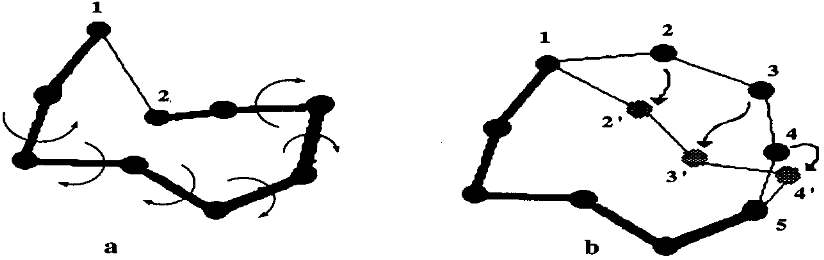

Figure 1. a. In **MULTIC**, rotating one ring bond distorts bond 1-2 and associated bond angles. Energy minimization is required after every step to fix the structure. b. In **Anneal-Ring**, three atoms 2,3 and 4 are exactly repositioned to create a new conformation with no bond length or bond angle distortion. Therefore no energy minimization is required.

Usually, ring conformation generation programs such as the **MULTIC** option of **Macromodel**[11] generate rings by systematic rotations around each possible bond (figure 1b), and only conformations with atoms 1 and 2 within approximate bonding distance, typically 1-3 Å, are kept. Full energy minimization of each new conformation is then required.

We felt that the smooth distortion of a ring model with no energy minimization (as is possible with a Dreiding model) would be a great improvement for existing methodology of ring conformational analysis.[12] The mathematical consequences of transforming one good conformation of a flexible ring into another good conformation, i.e. keeping all of the bond lengths and bond angles of the molecule at standard values, are a set of six nonlinear simultaneous equations in six unknowns.[13] Solving for the six dependent dihedrals to create a new conformation requires repositioning three atoms of the old conformation. For example, in figure 1b the exact recalculating and repositioning of atoms 2, 3 and 4 creates a new conformation with no bond length or bond angle distortion. Hence, unlike other conformation generation methods, no energy minimization during an **Anneal-Ring** run is required.

Discussion and Results

A cyclic molecule with N flexible dihedrals, contains N-6 dihedrals which can be considered independent random variables, and six dihedrals which can be considered dependent variables. Technically, the mathematical problem of converting one conformation of a flexible ring into another conformation while keeping the bond lengths and bond angles constant, is a mapping of N-6 independent random variables into six dependent variables. Therefore, up to N-6 dihedrals may be independently varied. Our "basic" **Anneal-Ring** algorithm is shown in figure 2. This algorithm generates a new conformation for the random walk by randomly picking and randomly rotating one dihedral θ, keeping constant all other independent variables. This moves atom 1. We then solve the nonlinear simultaneous equations for the six dependent flexible dihedrals ω_1 - ω_6 to reposition atoms 2, 3, and 4 and exactly reclose the ring. The molecular mechanics energy of the old and the new conformations are calculated, and these two structures are subjected to the Metropolis Monte Carlo accept-reject criterion [$\exp(-\Delta E/RT)$].[7] This process is repeated as the temperature is gradually reduced. As the temperature falls, the high energy regions of conformation space become inaccessible and the run ultimately converges to the global, or one of the low energy minima. For a more extensive discussion of the principles of simulated annealing the reader is referred to references 5c and 5d.

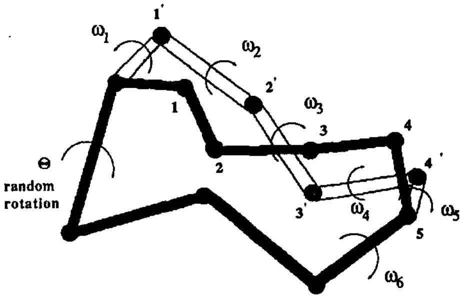

Figure 2. **The Single Step Anneal-Ring Algorithm.** Random rotation θ causes the displacement of atom 1. The next six dihedrals ω1 - ω6 are updated, repositioning atoms 2, 3, and 4, to reclose the ring with no bond angle or bond length distortions.

In order to test **Anneal-Ring**, a grid search[14] on cyclononane (C9), cyclodecane (C10), and cycloundecane (C11) was performed using **MULTIC** to prepare a database of all the low energy conformations of these rings; and specifically to locate the global minimum of each (table 1).

Table 1. Grid Search Using **MULTIC**

Cyclo-- alkane	MULTIC Dihedrals (N-3)	6^{N-3} Confs (theory)[a]	6^{N-3} Confs (actual)	Energy[b] global	Cputime[c]
cyclononane	(6)	46656	160	95.30	4 hr
cyclodecane	(7)	279936	691	99.09	17 hr
cycloundecane	(8)	1679616	1834	98.32	7 d 5 hr

a. The theoretical number of conformers for an N-membered ring needed for a systematic search at 60° resolution using **MULTIC**[14], assuming no rotation around terminal atoms. Ring conformers are treated like acyclic molecules with a bond broken open (i.e. N-3 rotatable dihedrals). **b.** MM2 Energies in Kjoul/mol
c. Microvax II.

Our basic (single rotation) **Anneal-Ring** program was then run on these rings. Twenty-five simulated annealing runs at 25 decreasing temperatures and 500 steps per temperature were done on C9, C10, and C11. The results collected in table 2. Twenty-five runs with various random starting geometries[9] found the global minimum twice for C9 and C10, and once for C11. Also note that other low energy conformations are hit as well, more

Table 2: Results of the "basic" Single-step **Anneal-Ring** algorithm[a]

	C9	C10[b]	C11[c]
Conformation #	Hits (out of 25)	Hits (out of 25)	Hits (out of 25)
1 (global)	2	2	1
2	11	3	1
3	3	2	
4	5	1	1
5			
6	4		
7		1	
8			
9		2	
10			
11		2	4

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a. Each run consisted of a total of 12,500 steps, 500 steps at twenty five different temperatures. The CPU time per run on a Vax 8600 was 7 minutes. **b.** Twelve other higher conformations were found for C10. **c.** Eighteen other higher conformations were found for C11.

frequently for the smaller systems. While it is gratifying to be able to hit the global minimum on all three rings using such a small amount of CPU time, the spread of conformations (table 2) obtained from multiple runs indicates incomplete searching. In theory, if the searches were sufficient, all runs would converge to the global minimum. Additionally, the results get worse as the ring gets bigger. All twenty-five runs of C9 converge to one of the six lowest conformations, while eighteen of the twenty-five C11 runs do not even converge to one of the eleven lowest conformations. The source of these problems is something that has been referred to as the "lever arm" effect.[15] Recall from figure 1b that to exactly reclose a ring to form a new conformation, three atoms must be repositioned. Our ring closure calculation uses several mathematical conditions including a parameter called vector **R** (figure 3) which is the vector distance spanning the three atoms (2, 3, and 4) whose positions must be calculated. The maximum length (absolute value of **R**) that three atoms can span is 5.04 Å if they are extended in an all trans arrangement. Therefore, if **R** is larger than 5.04 Å, ring closure is impossible.

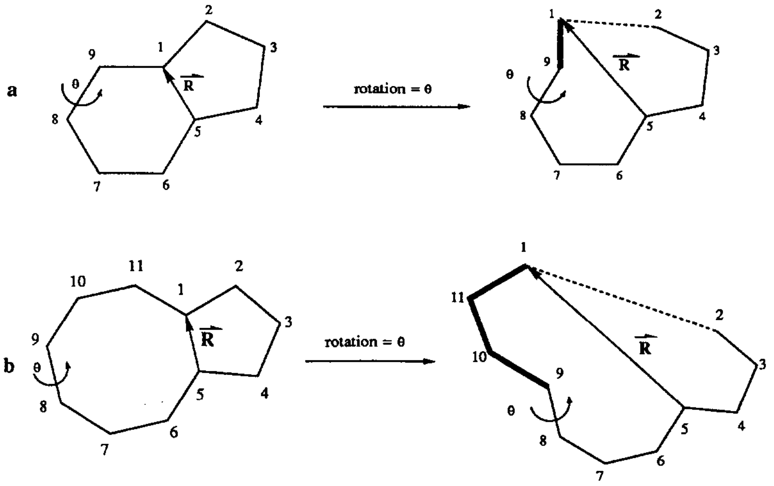

Figure 3. **The "lever arm" effect.** The variation of vector **R** as a function of random rotation θ and ring size. Atoms 2, 3 and 4 must be recalculated and repositioned. **a.** C9. **b.** C11.

This explains why our basic (single rotation) **Anneal-Ring** algorithm breaks down with larger rings. As we increase the ring size from C9 to C11 (figure 3, a vs b), the independent piece (demarcated in boldface in figure 3) gets larger, while the dependent piece remains constant. Therefore, for a given random rotation, the arc swept out by the independent part of the ring measured by the vector **R** in figure 3 gets larger as the ring size gets larger. As the vector **R** approaches and exceeds the ring closure limit, ring closure becomes less and less probable. A plot of vector **R** versus random rotation (data not shown[17]) shows that small variations of an independent dihedral in C11 brings the end-to-end closure distance either at or above the closure limit, while the same variations in C9 leave at least part of the curve reasonably below the closure limit. This "lever arm" effect causes the acceptance rate during a single step **Anneal-Ring** run to drop from a few percent in C9, to less than one percent in C11. The low and decreasing acceptance rate is responsible for the incomplete sampling of C9, C10, and C11, and the worsening results in going from C9 to C11.

The Multistep Algorithm.

To deal with the breakdown of the basic algorithm, we have added an option called **Multistep** to the **Anneal-Ring** package. **Multistep** (figure 4) performs successive random rotations on other independent dihedrals until vector **R** is within ring closure range. After initial random rotation the closure distance (the magnitude of the vector **R** in figure 3) is calculated to see if it is within range. If not, the structure is passed to **Multistep** and one or more additional independent dihedrals are varied until vector **R** is brought into range.

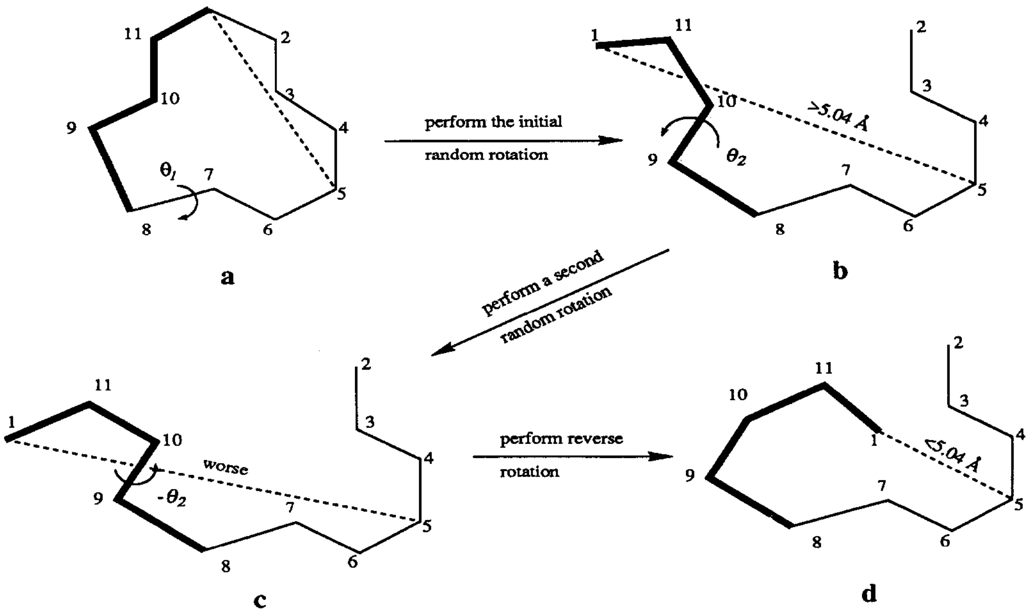

Figure 4. **The Multistep Subroutine. a.** The random selection of bond 7-8 for the initial random rotation θ_1, divides the ring into an independent part (atoms 8, 9, 10, 11, 1 bold), and a dependent part (atoms 2-7). The absolute value of Vector **R** defines a necessary condition for ring closure. **b.** After doing the random rotation, Vector **R** is greater than 5.04 Å. Therefore, no solutions will exist for the ring closure. **c.** A second random dihedral is chosen and a second random rotation (θ_2) worsens the situation. **d.** The reverse rotation (opposite sign rotation of the same dihedral ($-\theta_2$)) brings atoms 1 and 5 within closure distance. The structure is passed to the ring closure subroutine and atoms 2, 3 and 4 are recalculated to close the ring.

This improved version of **Anneal-Ring** was rerun on C9, C10, and C11, as well as on the much more challenging C17, (table 3). For C9, C10, and C11, the global minimum was now found in five out of five runs. The program was then tested on cycloheptadecane (C17). A recently published exhaustive search for conformations of C17 provided a database for comparisons.[16] The 17 dihedral angles of C17 provides a complex conformation space so that "cycloheptadecane lies close to the boundary distinguishing problems that can and cannot be addressed with contemporary methodology and resources."[16]

Table 3: Results of the **Anneal-Ring** algorithm with **Multistep**[a]

	C9	C10	C11	C17[b]
Conformation #	Hits	Hits	Hits	Hits
1 (global)	5	5	5	3
2				2

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a. Each run for C9-C11 consisted of a total of 12,500 steps, 500 steps at twenty five temperatures. The CPU time per run on a Vax 8600 was 1.2 hours.**b**. Each run for C17 consisted of a total of 100,000 steps, 4000 steps at twenty five temperatures. The CPU time per run on a Vax 8600 was 8.4 hours global minimum was now encountered in five of five runs.

Using **Anneal-Ring** with **Multistep** the global minimum of C17 was encountered in three out of five runs (table 3). Because of the size and complexity of C17 we found that a longer run was required. Since 100,000 steps were done on each C17 run (table 3), and the global minimum was encountered on every other run, this indicates that at least 200,000 steps may be required to satisfactorily search the conformation space of C17.

Methods

General: Starting geometries were built using the interactive modeling program Macromodel Version 1.0.[11] Initial and final geometries were energy minimized using versions of the MM2 force field as implemented in Macromodel (see ref 11).

Databases of low energy conformers: Low energy conformers of C9, C10 and C11 were obtained in the usual way using the **MULTIC** option[14] of Macromodel by designation of a closure bond and conformer generation at 60^o resolution keeping all conformers whose closure distance was within 1-3 Å. Minimization of resulting conformers used MM2 as implemented in Batchmin Version 1.0[11]. The C17 molecule is beyond the capabilities of the **MULTIC** tree search. Clark Still (Columbia University) provided us with the low energy database of C17 as reported in ref 16.

Simulated Annealing: Annealing was carried out on randomly selected staring geometries as described for acyclic compounds in ref 5d. The control file used for a typical **Anneal-Ring** run is similar to the one described in detail in reference 5c. The standard control data settings for C9 are: 3, 1, 1234, 1 = random number seeds; 100, 5, 25 = steps, blocks, temperatures; 0.10000, 5.00000, 1.10000 = starting temperature, step size, cooling factor; 1 = multistep option on; 0.5 = step size cut; 1= number of runs; 1 = force field (1= MM2, 3= Amber); 9 = ring atoms; 9 = rotatable bonds. A listing of the atom numbers for the rotation sets are also provided. More details may be found in reference 17. Source code for the program is available.[18] The runs described in tables 2 and 3 used the standard control data except as noted. The overall acceptance rates for the C9, C10 and C11 using basic "single step" annealing were ~5%, ~4% and ~1% respectively. The low acceptance rate was due to failure of new geometries to satisfy the initial math conditions (value of vector **R**, figure 3) for the existence of a solution to the Go-Scheraga ring equations. Consequently, subroutine **Ring** was rarely called and consequently the CPU time was quite short because few Monte Carlo moves were actually considered.

Multistep Option: With the subroutine **Multistep** turned on, the ring subroutine is not called until one or more rotations bring atoms 1 and 5 within the ~5.04 Å range for a Go-Scheraga solution to exist. Using this option, the overall acceptance rate is now ~40%. This means that an adequate search of the conformation space may be done. A description of the operation of **Multistep** on C17 is given in (table 5) for a few steps of the search. Entry 1 shows the value of vector **R** (cf. figure 4) after the first random rotation. Subsequent entries show the value of **R** as **Multistep** searches for a good ring closure. For the first step, the value of the **R** is clearly out of the 5.04 Å ring closure range (entry 1, 6.55Å). Therefore, a second independent dihedral is randomly selected and randomly rotated. This rotation pushes the absolute value **R** farther out of range (entry 2, 6.88Å). At this point **Multistep** performs the exact opposite rotation of this same dihedral (back rot in table 4). This makes the situation better, but the ends are still not within closure range (entry 3, 6.21Å). Therefore a third independent dihedral is randomly chosen and randomly rotated. Again this exacerbates the situation (entry 4, 9.31 Å). The reverse rotation again makes the situation better, but not good enough (entry 5, 5.21 Å). Finally, the third random rotation brings the absolute value of **R** into closure range (entry 6, 4.78 Å) and the structure is ready to be passed to final ring closure subroutine. The second step, after the initial random rotation, is also out of closure range (entry 1, 8.61 Å). Since subsequent random rotations keep improving the situation, there is no need for back rotation. In the third step, the value of **R** does not come into closure range after five additional tries.

Table 4. The Multistep Option: Variation of Vector **R** during Conformation Generation

Entry	Rotation	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
1	New **R**	6.55	8.61	7.86	**4.05**[b]	5.21	8.59
2	new rot 1[a]	6.88	7.94	8.43		7.65	7.33
3	back rot 1	6.21	----	7.22		5.67	----
4	new rot 2	9.31	7.52	8.87		7.04	5.63
5	back rot 2	5.21	----	5.33		10.51	----
6	new rot 3	**4.78**[b]	**3.56**[b]	9.07		8.50	7.25
7	back rot 3			6.51		----	11.17
8	new rot 4			9.52		6.21	**4.31**[b]
9	back rot 4			6.21		----	
10	new rot 5			9.24[c]		10.70[c]	

Note: each column labeled step represents one attempt at a Monte-Carlo move. Thus with our standard control file used here (500 steps at 25 temperatures) there were 500 such attempts to find a new ring. For each step we allow 10 trials (i.e. entry 1-10) in the search for a possible new ring for each step. **a.** rot = rotation. **b.** Once a conformation is found with vector **R** within range, the coordinates are passed to the ring calculation subroutines for ring closure. Only then is simulated annealing done. **c.** No conformation found after five trials. The program returns to the previous geometry.

Therefore, this whole move is discarded and the program returns to the same conformation at step 2. The fourth step is within closure range after the initial random rotation, so there is no need to call **Multistep**. Steps 5 and 6 in the table continue is the same way.

Anneal-Ring: Detailed description of our program for simulated annealing of flexible acyclic molecules has been reported.[5c,d] Essentially, doing simulated annealing of flexible rings requires a procedure which will randomly generate undistorted conformers of these rings rapidly. The Go-Scheraga[13] ring closure program (QCPE #397) lays out the functional interdependence of the rotatable dihedrals in a flexible ring as a mapping F:n-6--->6. This formulation in internal coordinates using a rigid geometry approximation gives rise to a set of six nonlinear simultaneous equations in six unknowns. Joining Go-Scheraga to our existing simulated annealing algorithm required redesigning the code (Figure 5).[19] Full details of the modifications of Go-Scheraga as a stand-alone ring deformation algorithm will be reported separately.[17] The operation of **Anneal-Ring** involves performing a random rotation in subroutine **Step** wherein the structure is distorted. The program enters algorithm **Close** which divides the ring into a dependent and independent part, calls subroutine **Parameter** to calculate vector **R** and then calls subroutine **Conditions** to see if the necessary ring closure conditions are satisfied. If the conditions are not satisfied, the program may pass into algorithm **Multistep** which calls subroutines **Rot_Again**, **New_Con**, and **Back_Rot** which perform subsequent rotations on the other independent

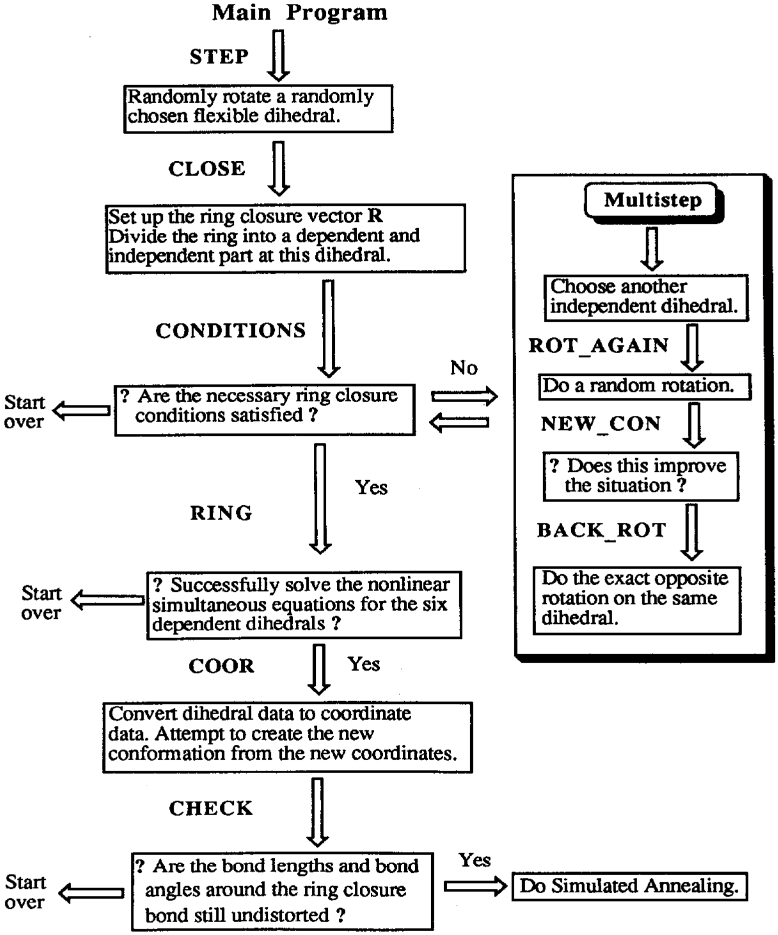

Figure 5: **Flow chart for Anneal-Ring (from ref 17)**

variables in an attempt to satisfy the ring closure conditions. When the ring closure conditions are satisfied, the program passes to the Go-Scheraga subroutine **Ring** which attempts to calculate new solutions. As soon as one solution is found, the program immediately leaves **Ring** and passes to subroutine **Coor** for conversion of the dihedral solutions into Cartesian coordinates. Before this new solution can be annealed, it must be verified as a true solution, because iterations of systems of nonlinear equations may give erroneous answers. The new conformer is passed to subroutine **Check** which makes sure that the bond lengths and bond angles around the closure point have actually been kept constant. If this new conformer is passes this final test, it is passed on to the annealing routines (cf. ref 5d). If not, the whole process starts over using the old conformer.

Conclusions

The deformation of rings is actually of broad significance. Deforming select flexible portions of a large molecule, while keeping other parts fixed, has direct application to many important chemical and biochemical processes such as the deformation of polymers, the movement of loops within proteins or unwinding of DNA. Often such problems are addressed nowadays with molecular dynamics (MD). As a conformation searching tool, however, MD is limited to only local searches and is extremely CPU intensive.[20]

We have successfully applied the simulated annealing method to the conformational analysis of hydrocarbon rings. The exact ring closure of rings allows the use of simulated annealing as an efficient method for searching for the global minimum. The algorithm's focus on location of the optimal configuration is an inherent weakness, however, because a complete set of low energy conformers are often of interest. We are currently developing options in the **Anneal-Ring** package to collect a complete set of conformations of a flexible ring. We are also expanding the package to be able to analyze problems of biochemical interest such as protein loops. These results will form the basis for future reports.

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18 Source code for **Anneal-Ring** is available for distrubution: contact Patrick Franc, NYU Industrial Liason Office, NYU Medical School, NY, NY. E-mail Address: Franc.cs.nyu.edu.

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