ANNEAL-RING: A New Algorithm for Optimization of Rings Using Simulated Annealing

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The exact calculation of the six dependent dihedrals in rings allows smooth deformation by computer and the application of simulated annealing to the location of the global minimum of rings.

Deforming an *acyclic* flexible structure by computer simply requires the rotation around any flexible dihedral angle.[1] Unique new complexities are added if one wants to deform cyclic structures. Rotating only one dihedral in a *cyclic* structure will inevitably distort one or more of the bond lengths and bond angles of the molecule. Usually, conformation generation programs generate ring systems by defining a closure bond and then consider the ring as if it were acyclic. Systematic rotation around each possible bond is done and only those conformations with closure atoms within approximate bonding distance are retained.[2] Full energy minimization of each new conformation is then required.

ANNEAL-RING generates new ring conformations by smooth distortion of a molecule as one might flex a Dreiding model. This requires consideration of the mathematical consequences of ring constraints. Keeping all of the bond lengths and bond angles of the molecule at standard values, means that a cyclic molecule with N dihedrals has only N-6 independent dihedral angles. Six dihedral angles are dependent variables. These six dependent dihedrals make up unknowns in a set of six nonlinear simultaneous equations.[3] Solving these equations allows us to create a new conformation by repositioning three atoms of the old conformation (Fig. 1). The new conformation requires no energy minimization.

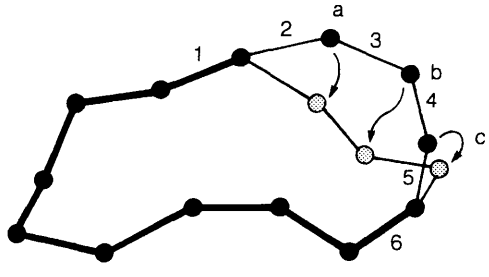

Fig. 1 Ring deformation requires that atoms a, b and c are moved by calculation of dependent dihedrals 1–6

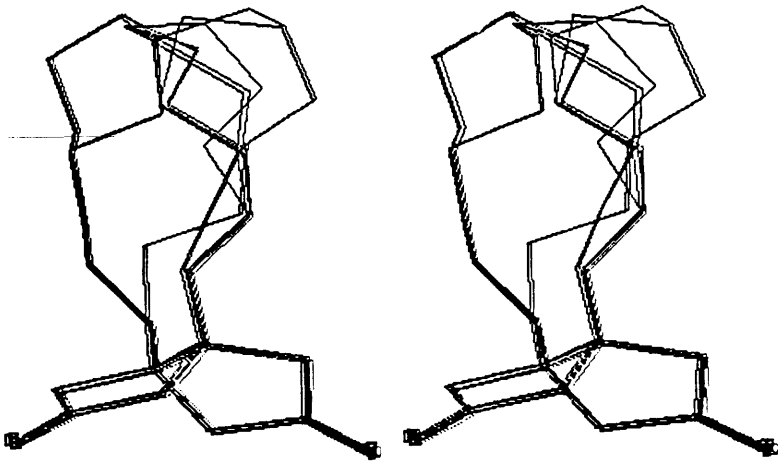

Fig. 2 Superposition of several conformers of 12.3.3-propellane produced by ANNEAL-RING (stereopair)

We have succeeded in adding this ring closure algorithm to our simulated annealing package, which allows us to study rings. We have recently applied the technique of simulated annealing to acyclic conformational analysis.[4] We must emphasize that to apply simulated annealing to rings we must be able to generate one new undistorted geometry so that the E_{cost} for a random move can be computed ($E_{cost} = E_{old} - E_{new}$).[4]

We now report the first results of the simulated annealing of rings. Our program ANNEAL-RING was run on cyclononane, cyclodecane, cycloundecane and cycloheptadecane (c9, c10, c11 and c17). The location of the global minimum of rings c9, c10 and c11 has been reported previously by Still.[2b] We also carried out a systematic conformation search for the global minimum of c9, c10 and c11 using the MULTIC option of MACROMODEL[5] [consuming 4, 17 and 173 central processing unit (cpu) hours, respectively on a VAX 8600]. The same global minimum was also found by ANNEAL-RING in all five runs.† A recently published[6] exhaustive search for conformations of c17 provides a recent review of conformation searching techniques and the global minimum of c17 (18.90 kcal; 1 cal = 4.184 J) for comparison. The 17 dihedral angles of c17 provides such a complex conformation space the authors state: 'Cycloheptadecane lies close to the boundary distinguishing problems that can and cannot be addressed with contemporary methodology and resources.' While c17 pushes contemporary methodologies to the limit, ANNEAL-RING finds the global minimum of c17 in three out of five runs in only 8.4 cpu hours on a VAX 8600.

The classic problem of ring deformation is actually of much broader interest. Deforming select flexible portions of a large molecule, while keeping other parts fixed, has important applications in biochemistry, since movement of loops within proteins is, in essence, the same problem. To demonstrate the method of local defomation, we have examined the bicyclic molecule 12.3.3-propellane.[7] The generation of new conformations of a bridged cyclic compound having 11 rotatable dihedral angles is quite difficult with currently available modelling software. Fig. 2 shows the superposition of several conformations of 12.3.3-propellane, generated with ANNEAL-RING. We are able to generate 154 completely undistorted new conformers of 12.3.3-propellane per cpu min on a VAX 8600 using ANNEAL-RING.‡

In conclusion, we have shown that rings can be deformed exactly and that simulated annealing using ANNEAL-RING is an efficient method for searching for conformations. The global minimum of several cyclic hydrocarbons can readily be found using this technique. Local deformation was also demonstrated. Extensions to protein loops as well as more detailed results will be reported elsewhere.[8]

We thank W. C. Still for providing us with the coordinates of the c17 global minimum as described in ref. 6.

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† Details of our acyclic simulated annealing algorithm (such as the cooling schedule. step size, etc.) are discussed in reference 4(*b*) and 4(*c*). Each ANNEAL-RING run for c9, c10 and c11 consisted of 12 500 MC steps, 500 steps at 25 temperatures with a cpu time per run of 1.2 h on a Vax 8600. Each run for c17 consisted of 100 000 MC steps, 4000 steps at 25 temperatures with a cpu time per run of 8.4 h.

‡ Vax source code for ring deformation using ANNEAL-RING is available on IBM or Macintosh disk as well as *via* BITNET. Contact the author at the above address or by e-mail: Wilsons@NYUACF.