

80:20 mixture, 63% overall yield.

(23a): mp 102–103 °C; $[\alpha]_D^{25}$ –28.28° (c 2.075, CHCl₃); IR (CHCl₃) 3420, 2940, 1700, 1470, 1420, 1370, 1350, 1150 cm⁻¹; ¹H NMR δ 4.57 (br d, 1 H, J = 9.9 Hz), 4.25 (br d, 1 H, J = 9.1 Hz), 3.70 (s, 3 H), 3.30 (s, 1 H), 3.14 (t, 1 H, J = 9.1 Hz), 2.51 (m, 2 H), 1.85 (m, 1 H), 1.43 (s, 9 H), 0.98 (d, 3 H, J = 6.8 Hz), 0.95 (d, 3 H, J = 6.8 Hz); ¹³C NMR δ 173.26, 156.29, 78.76, 66.84, 59.54, 51.45, 39.05, 29.99, 28.17, 19.53, 19.29; MS *m/e* 232, 202, 172, 132, 116, 100, 72, 57; exact mass calcd for C₁₃H₂₅NO₅ 275.173, found 275.173.

(23b): ¹H NMR δ 4.42 (br d, 1 H, J = 9.5 Hz), 3.93 (m, 1 H), 3.72 (s, 3 H), 3.52 (m, 1 H), 3.24 (br, d, 1 H, J = 4 Hz), 2.53 (m, 2 H), 2.12 (m, 1 H), 1.44 (s, 9 H), 0.95 (d, 3 H, J = 6.9 Hz), 0.88 (d, 3 H, J = 6.9 Hz); ¹³C NMR δ 173.50, 156.35, 79.49, 69.21, 58.87, 51.70, 38.26, 28.29, 27.50, 20.08, 16.19.

(4S,5S)-4-Hydroxy-5-isopropyl-2-oxopyrrolidine (24a). To 352 mg (1.28 mmol) of 23a was added 4 mL of 3 M HCl/ethyl acetate solution. The reaction was stirred at room temperature for 30 min. After neutralization with a saturated sodium bicarbonate solution, the solvents were evaporated, and the residue was washed with acetone. These layers were concentrated and purified by flash column chromatography (75% acetone/hexane) to give 24a as a crystalline compound: mp 127–129 °C; $[\alpha]_D^{25}$ –11.03° (c 0.825, MeOH); IR (CHCl₃) 3450, 3400, 2990, 1700, 1400 cm⁻¹; ¹H NMR (CD₃OD) δ 4.38 (t, 1 H, J = 4.52 Hz), 3.22 (dd, 1 H, J = 4.3, 9.3 Hz), 2.64 (dd, 1 H, J = 5.6, 17.0 Hz), 2.20 (d, 1 H, J = 17.0 Hz), 1.96 (m, 1 H), 1.03 (d, 3 H, J = 6.6 Hz), 0.98 (d, 3 H, J = 6.6 Hz); ¹³C NMR (CD₃OD) δ 179.44, 68.94, 67.97, 42.61, 28.44, 20.35, 19.44; MS *m/e* 143, 128, 114, 100, 83, 72, 55; exact mass calcd for C₇H₁₃NO₂ 143.095, found 143.094.

(3S,4S)-Methyl 4-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-6-methylheptanoate (25a). A solution of 12a (50 mg, 0.16 mmol) in dichloromethane (10 mL) and methanol (1 mL) was cooled to –78 °C and ozone was bubbled through the solution until the blue color persisted. The reaction was purged with nitrogen to remove the excess ozone, and sodium borohydride (6.05 mg, 0.16 mmol) was added at –78 °C. The reaction was warmed to room temperature and stirred for 5 h. The same workup as described for 23a was followed. After HPLC (Whatman Partisil M9 10/50, 30% ethyl acetate/hexane) 24 mg (52%) of 25a (white solid) and 6 mg (10%) of 26a were obtained. Treatment of 26a

with sodium methoxide in methanol (3.0 equiv, room temperature, 6 h) afforded quantitatively 25a. 25a: $[\alpha]_D^{25}$ –36.8° (c 1.0, EtOH), (lit.^{1a} $[\alpha]_D^{25}$ –37.6°, (c 1.0, EtOH)); IR (CHCl₃) 3480, 3000, 1730, 1520, 1460, 1390, 1270, 1180 cm⁻¹; ¹H NMR δ 4.71 (br d, 1 H, J = 9.3 Hz), 4.02 (m, 1 H), 3.71 (s, 3 H), 3.61 (m, 1 H), 3.26 (br s, 1 H), 2.54 (m, 2 H), 1.70 (m, 3 H), 1.44 (s, 9 H), 0.93 (d, 6 H, J = 6.5 Hz); ¹³C NMR δ 173.44, 155.99, 79.00, 69.64, 52.00, 51.64, 41.54, 38.62, 28.23, 24.64, 22.93, 22.15; MS *m/e* 216, 186, 176, 158, 142, 130, 86, 57; exact mass calcd for C₁₄H₂₇NO₅ 289.187, found 289.188.

Stereochemical Determination of 10a and 10b. To 112 mg (0.367 mmol) of 9a (or 9b) in methanol (8 mL) was added 67 mg of 10% palladium–carbon followed by 1 mL of cyclohexene. The reaction was refluxed for 2 h and then filtered, washed with methanol, and concentrated. The crude product was dissolved in chloroform (8 mL) and 81 mg (0.37 mmol) of di-*tert*-butyldicarbonate was added. The reaction was stirred at room temperature for 12 h. The solvent was evaporated and the residue diluted with ethyl ether. The organic phase was washed sequentially with 0.5 M H₃PO₄, 1 M NaHCO₃, and brine. Concentration of solvents and purification by flash column chromatography (60% ethyl acetate/hexane) gave 10a (or 10b) as an only isomer.

Stereochemical Determination of 13b, 14a, 14b, and 15b. The same procedure as described before was followed. Deprotection of the dibenzyl group by catalytic transfer hydrogenation and protection of the amino group as *t*-Boc [2-[[(*tert*-butyloxycarbonyloxy)imino]-2-phenylacetoneitrile (Aldrich, BOC-ON)] afforded 10b, 11a, 11b, and 12b, respectively.

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Supplementary Material Available: General experimental and characterization data for compounds 9b, 10a,b, 11a,b, 12a,b, 13b, 14a,b, 15b, 16a,b, 18a, 19a, 24b, 25b, and 26a (8 pages). Ordering information is given on any current masthead page.

A New Approach to Probing Conformational Space with Molecular Mechanics: Random Incremental Pulse Search

David M. Ferguson and Douglas J. Raber*

Contribution from the Department of Chemistry, University of South Florida, Tampa, Florida 33620. Received September 8, 1988

Abstract: A computational method is described that permits reliable searching for different molecular conformations. A Monte Carlo type routine is employed to randomly search the potential energy surface for a given molecule, and Allinger's MM2 force field is employed for energy calculations and minimizations. The method has two modes of operation: conformational search (by torsional or energetic criterion) and global minimum location. The Monte Carlo type routine, called random incremental pulse search (RIPS), logically couples the benefits of random searching with those of analytical minimization. The method has been tested by searching conformational space for a series of cycloalkanes. All conformational families and minimum-energy structures are reliably located in each case.

During the last decade the computation of molecular structure has become a standard tool of organic chemists,^{1–3} and molecular mechanics has proved to be an extremely powerful technique for this purpose.^{3–5} Until recently almost all efforts in this area have

focused on minimizing the energy of a trial geometry that is supplied by the investigator, but it has become increasingly important to evaluate the molecular geometries and energies of other structures as well.^{6,7} Two specific problems are particularly

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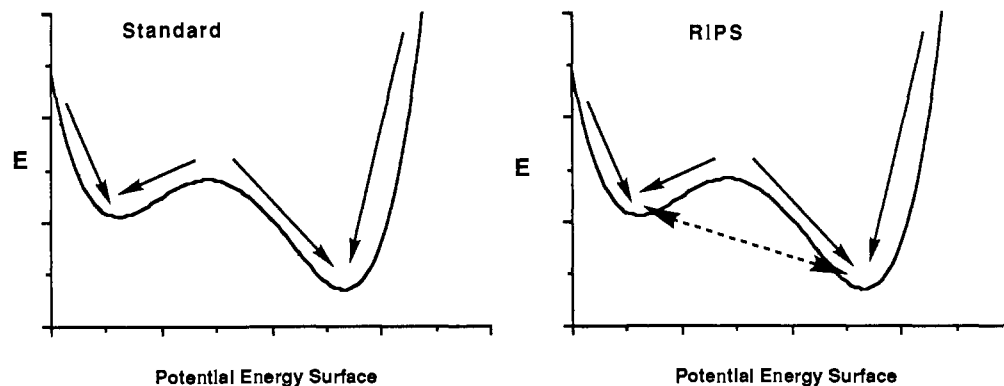


Figure 1. A schematic comparison of standard vs RIPS algorithms for energy minimizations. Standard methods can only proceed downhill on the potential energy surface, whereas the RIPS method allows crossing of energy barriers.

important: to determine the global energy minimum (i.e., the most stable conformation) and to locate other energy minima on the potential energy surface. The standard algorithms for energy minimization in the commonly available molecular mechanics programs are mainly limited to downhill-energy searches.³ As a consequence, the energy and structure obtained in an optimization procedure are highly dependent upon the input geometry that is employed. Clearly, optimization will afford only a single energy-minimized structure. However, that structure may not correspond to the global minimum and there may be multiple minima on the conformational surface.

In order to address the problem of multiple minima, strategies must be fashioned to search the conformational space available to molecular systems. In most cases trial geometries are generated that represent the starting point for molecular mechanics optimization. These starting points must exhibit sufficient geometric variation to afford conformational interconversion upon optimization. Systematic methods have been devised that vary internal coordinates^{8,9} and interatomic distances.¹⁰ Although these methods are most frequently employed, stochastic methodology is also well suited to explore the potential hypersurface of molecules. Random methods should not suffer from external bias, whereas systematic routines frequently do.

The use of a stochastic method to explore conformational space was first reported by Li and Scheraga.¹¹ The routine employed the Metropolis method¹² to sample potential conformations for allowed energy transitions, thus providing a dynamic constraint to the search. Internal coordinates (torsion angles) were randomly incremented to provide conformational interconversion. The method was applied successfully to locate the lowest energy conformer of a pentapeptide. A related method has been employed to locate all conformations that contribute to the equilibrium mixture and was found to yield satisfactory results when applied to a variety of organic systems.¹³ A brief communication describing a stochastic method based on external coordinate (Cartesian) variation has been reported by Saunders,¹⁴ but no detailed discussion of the results or characterization of the method was presented. Concurrently with these advances in stochastic methodology a new random routine based on Cartesian coordinate variation was developed in our laboratory. The complete characterization and demonstration of this method, which incorporates

Allinger's MM2 program,^{15,16} is reported in this paper.

Development of the Program

As part of our studies of metal complexes with molecular mechanics, we discovered that energy minimization of 7-coordinate lanthanide complexes with our modified MM2 program afforded structures with geometries that were nearly the same, but not identical with, the structures determined by X-ray crystallography.¹⁷ Further investigation of various other 7-coordinate lanthanide complexes yielded similar results,¹⁸ and we found that different starting geometries sometimes converged to different energy minima. Clearly, there were multiple minima on these MM2 potential surfaces, and our previously reported approach¹⁷ did not always afford the global energy minimum. Figure 1 depicts the standard energy-minimization procedure (downhill only) along with the approach that is needed in order to breach local energy barriers in the path to the global minimum.

Our first efforts to solve this problem employed successive coordinate truncation²³ and minimization. The truncation procedure involves taking the output geometry of a minimized structure and truncating the *x*, *y*, and *z* coordinates for each atom to two or three decimal places, thereby introducing small, semirandom changes in the positions of the individual atoms. This moves the structure to a new location on the potential energy surface, a location that is no longer at an energy minimum. Analytical minimization now affords the possibility for downhill searching to afford a new minimum-energy structure. Using this technique for lanthanide complexes, we noted that steric energies were slightly lower than those obtained by a single optimization of the input coordinates.

Once we had ascertained that small perturbations in atomic coordinates would allow energy minimization to proceed further downhill, a more general procedure was developed that could be integrated with our existing MM2 program with its metal-extended force field (MM2MX).¹⁷ A pseudo-Monte Carlo approach was employed in which random changes in the positions of each atom (or a specified subset of atoms) could be used to perturb the input geometry. While the Monte Carlo approach has been widely employed in computational chemistry,²⁰⁻²² there have been a limited number of applications that combine this technique with analytical minimization.^{11,13,14} In principle, the development of

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this random procedure should be quite simple, but several questions require careful consideration. Are the perturbations truly random? Will all conformations be located? How will new (unique) structures be recognized? Finally, how can the procedure be carried out most efficiently? The approach to resolving these problems is discussed in the following paragraphs.

Are the Perturbations Truly Random? Our initial calculations employing truncation of the input coordinates demonstrated the feasibility of obtaining structures of lower energy by carrying out successive minimizations, but the perturbations in atomic coordinates were not random. Truncation necessarily moves each atom toward the origin of the coordinate system, so the various motions are correlated. This problem was solved by using a uniform random number generator¹⁹ to add random increments to the *x*, *y*, and *z* coordinates of each atom. The user specifies the maximum step size, which corresponds to the maximum displacement of any atom in a direction parallel to one of the axes. However, the net displacement in an off-axis direction can exceed this maximum, so there is some dependence of atomic displacements on the orientation of the structure with respect to the coordinate system. However, the molecule is allowed to "float" with respect to the coordinate system during successive minimization steps, so the net perturbation becomes independent of any bias initially created by the molecular orientation.

Will All Conformations Be Located? True local minima are minimized with respect to all degrees of freedom; saddle points and higher order stationary points are possible transition states for interconversion between conformations.^{3,24,25} The block diagonal Newton Raphson method that is employed in the MM2 program will converge on minima and first-order stationary points.³ In contrast to full-matrix Newton Raphson minimization, this modified technique does not always converge on saddle points; furthermore, the trial geometry must be close to that of the transition state for analytical convergence to occur.³ The block diagonal Newton Raphson minimization converges rapidly on minima from poor starting geometries but tends to slow or to terminate prematurely as the minimum is approached. The latter problem is magnified for molecules that have flat potential surfaces.³

The stochastic method that is employed in this study generates trial geometries that may be located anywhere on the hypersurface. Analytical minimization will yield minima and saddle points, but the former will be located with much higher probability. The ability of the search to find all possible structures depends on the completion criteria for execution. Clearly, there is no explicit test to determine whether or not a random method has located all minima. It would be possible to calculate a relative probability that all minima have been found for a given search, but a much simpler approach has been adopted. The search is terminated after the number of unsuccessful attempts has reached a user-defined *termination number*. The appropriate value will vary with the size and type of molecule being investigated. However, the completion of a search by this criterion does not guarantee that all minima have been located.

How Will New (Unique) Structures Be Recognized? When a minimum-energy structure is generated, it is of no value unless it is different from all other structures previously found. Consequently, the program must discard duplicate structures. However, when the same conformation is generated in two different energy minimizations, the probability that the atomic coordinates will be identical is extremely small, even if the two structures are placed in the same orientation via translation and rotation. Saunders compared the interatomic distance matrix for the two structures,¹⁴ but as with any method of mathematical comparison, one must specify some limit, below which two nonidentical distances will be considered equivalent for the purposes of the comparison.

Two criteria have been utilized for deciding whether or not two geometry-optimized structures are the same. The first criterion

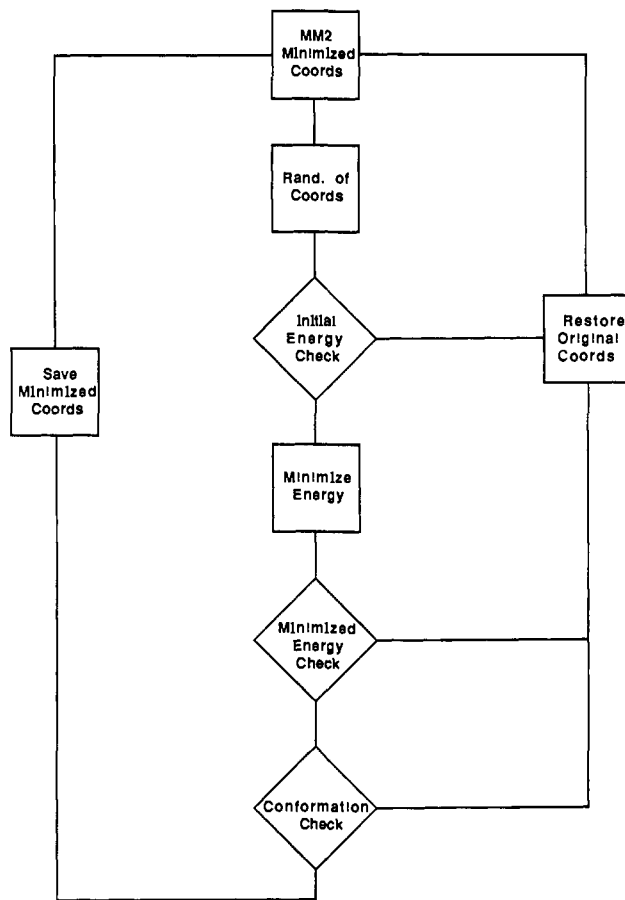


Figure 2. The architecture of the RIPS program.

is simply the energy. If the energy of a new geometry differs by some minimum (user-specified) value from that of the previous geometry, then it is considered to be a different structure. This test can be carried out very quickly, but it cannot distinguish between structures that might be symmetry related or might by coincidence have nearly the same energy. The second criterion for distinguishing between nonidentical structures is based on the fundamental definition of conformation:²⁶ conformations differ by rotations about single bonds. Two distinct conformations must exhibit at least one difference when comparing lists of all dihedral angles involving bonded atoms. The appropriate list is generated by the standard MM2 calculation, and it is used accordingly. Dihedral angles of all non-hydrogen atoms are evaluated, thereby avoiding such problems as describing methyl rotamers as different conformations. The user can set a threshold value, and any single dihedral angle difference above this threshold when the lists are compared will cause a decision that the two structures are non-equivalent.

Program Design

The approach discussed above has been implemented in our random incremental pulse search (RIPS) program, which in turn uses the subroutines from MM2¹⁶ (or more specifically our modified version, MM2MX¹⁷). The program can be used in either of two modes, *Global Energy Minimization* and *Conformational Search*, and any optimized structure may be subjected to further refinement. The program architecture is summarized in Figure 2.

Global Energy Minimization. The overall scheme begins with a normal MM2 optimization of the user-supplied coordinates, and this energy minimization affords the *current coordinates* that will be used as the input data for subsequent calculations. The first *pulse* is initiated, beginning with a *randomization* step in which the *x*, *y*, and *z* coordinates of each specified atom (the default

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is all atoms) in the molecule are perturbed individually by addition of a random increment uniformly distributed between $\pm\delta$, where δ is user specified.

The resulting *trial input coordinates* are not immediately subjected to energy minimization but are first evaluated with the initial energy routine of MM2. In order to screen out unreasonable starting geometries produced by randomization, the user defines an *initial energy window* by specifying upper and lower limits. If the energy of the trial input coordinates does not fall inside the initial energy window, that set of coordinates is discarded and the program returns to the randomization step with the previously minimized current coordinates. The program continues in this loop until it generates a set of trial input coordinates that meet the criterion of the initial energy window. At this point a full energy minimization of the trial input coordinates takes place.

Energy minimization of the trial input coordinates produces a set of *minimized trial coordinates*, which are subject to two tests to determine whether or not the program has completed a *successful pulse*. The first test is a *minimized energy check*, which compares the energy of the minimized trial coordinates with that of the current coordinates. The energy check is satisfied if the newly minimized energy is lower.

The second test is a *chirality check*. When the maximum step size for random movement of any single coordinate is in the range of 0.5–1.0 Å, the total displacement of an atom could be as large as 0.9–1.7 Å, a range that includes the interatomic distances for two atoms (hydrogen or carbon) both bonded to the same carbon atom. Randomization can therefore produce interchange of two substituents on a single atomic center, a result corresponding to a change in chirality of that center that we have called a *mechanical inversion*. Since the descriptor (i.e., atom number) is unique for every substituent bonded to a tetravalent atom, each such center can be assigned a chirality. A chirality list is generated for all tetravalent carbons (or for a user-specified subset), and this is compared with the corresponding chirality list of the trial coordinates. If there is any discrepancy between the lists, there has been a mechanical inversion with failure of the chirality check. Of course, there may be instances in which one wants to generate inverted centers, and the chirality check can be suppressed for specific atoms (or all atoms).

If both the energy check and chirality check are satisfied during a global optimization, the program has completed a successful pulse. The existing set of current coordinates is replaced by the minimized trial coordinates (along with its corresponding energy), and a new pulse is initiated. When either the energy check or the chirality check fails, the program has completed an *unsuccessful pulse*. After an unsuccessful pulse the program also initiates a new pulse; the newly generated set of minimized trial coordinates is discarded, and the program restores the existing current coordinates. Execution continues through a series of pulses that may or may not continue to generate new structures of lower energy. Completion of N consecutive unsuccessful pulses (where N is the user-defined termination number) constitutes logical termination of the RIPS sequence; execution stops and the search summary is written to disk. Whether or not the global minimum will actually be found with this probabilistic search strategy is dependent upon the various user-defined parameters that are employed.

Conformational Search. The basic procedures in the RIPS program are the same for both global minimization and conformational search. The goal of the latter scheme is to locate and catalog each of the available conformations within a certain energy limit. This limit may be a static *minimized energy limit*, specific relative to the global minimum, or some other arbitrarily defined MM2 steric energy. A dynamic *minimized energy tolerance* may alternatively be specified relative to the current energy, providing a limit that would change during the course of the run and facilitate uphill energy searching. In addition, a successful pulse in the conformational search mode must also meet one of the following two criteria.

(1) Conformational Energy Criterion. The structure must differ from all previously located conformations by a user-defined

conformational energy tolerance. This allows a search of the conformational surface entirely on the basis of energetics. When the conformational energy tolerance criterion is employed, it is not possible to locate two conformations that have nearly identical energies (either by coincidence or as a consequence of symmetry). On the other hand, equivalent structures are not duplicated.

(2) Dihedral Angle Criterion. The MM2 dihedral angle list for the minimized trial coordinates is compared with the corresponding lists for all previously located conformations. The structure is considered to be a new conformation if there is at least one dihedral angle difference greater than the user-specified *dihedral-angle tolerance*.

When a successful pulse has occurred, execution continues in the following way. First, the existing set of current coordinates is replaced by those of the newly determined minimum. Second, the coordinates for the newly located minimum are added to the catalog of energy minima. Third, a new pulse is initiated, and the program continues until the termination number criterion is met.

Refinement. When an energy minimum lies on a relatively flat portion of the potential surface, minimization can end before the lowest energy point is located. In such situations minimizations from different starting geometries will not converge on the same optimized structure, even though the final energies may be virtually identical. Previous studies have found dihedral differences to be as much as 10° .³ To circumvent this problem a subsearch refinement procedure has been added that is carried out following successful completion of the chiral check. The minimized trial coordinates are subjected to small random increments (the maximum increment is user defined with a default value of 0.05 Å) followed by energy minimization. This very small perturbation of the atomic coordinates does not displace the structure from the local potential energy well but causes sufficient distortion to allow minimization to proceed to the true local minimum. Refinement is considered successful if the new energy is less than the starting energy; the newly minimized coordinates replace the current coordinates, and another refinement pulse can be carried out. The trial coordinates are discarded for unsuccessful refinement pulses, and the current coordinates remain unchanged. Refinement is terminated following a user-specified number of unsuccessful refinement pulses.

Wiberg employed a similar technique to check for complete optimization, although his coordinate movements were arbitrarily defined;²⁷ local minima were reproduced with confidence using this procedure. A related method to test optimized geometries to saddle points has also been reported.^{3,28,29} A structure that is a suspected transition state is geometrically perturbed and then optimized. Generation of a new structure by this procedure indicates that the original was a saddle point. The ability of our RIPS program to carry out such tests provides a valuable addition to its capabilities for locating minimum-energy structures.

Results and Discussion

In order to test and demonstrate the RIPS method, we have investigated a series of hydrocarbons for which extensive conformational studies have previously been reported. Conformational (energy and/or dihedral criterion) and global searches were carried out for each of these compounds. Our results are reported to more decimal places than would normally be justified for molecular mechanics calculations, but this is necessary for comparison of the various results. For cycloalkane conformations the nomenclature used by Hendrickson has been employed.^{30–33} Calculations were performed on an IBM 3081 mainframe computer, and the program has been installed on both MVS and VM/CMS operating systems.

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Table I. Data for Butane^a

criterion	conformation	C1-C2-C3-C4	
		dihedral angle	energy
dihedral with refinement	anti	180.00	2.1714
	gauche	-65.20	3.0348
energy with refinement	gauche	65.16	3.0348
	anti	180.00	2.1714
	gauche	65.19	3.0348

^aEnergies in kilocalories/mole; angles in degrees.

Each reported search corresponds to a single complete run rather than to a combination of several separate searches. It may frequently be beneficial to combine the results of several searches, but our goal here was to define the scope and capabilities of a new method. No single set of the various user-defined parameters is optimal for all compounds, and values were employed that afforded the best results with each compound studied. A coordinate increment of 1.0 Å was found to give good results and was employed in all searches. Termination numbers ranged from 100 pulses for butane to 500 pulses for more conformationally complex systems such as cyclooctane. Initial energy windows were set with a minimum value of 0.0 kcal/mol and a maximum value 5–10 times larger than the MM2 steric energy of the global energy minimum. The dihedral angle tolerances ranged from 6° to 12°, the larger values becoming necessary for more flexible ring systems. Energy refinements were carried out using maximum coordinate increments of either 0.01 Å or 0.05 Å. The latter was generally the most efficient, while the former value worked best in global searches. Most of the compounds in this study were symmetrical cycloalkanes (CH₂)_n, and mechanical inversion could only interchange two hydrogen atoms. In order to reduce the computation time with more complex systems (cyclooctane), the

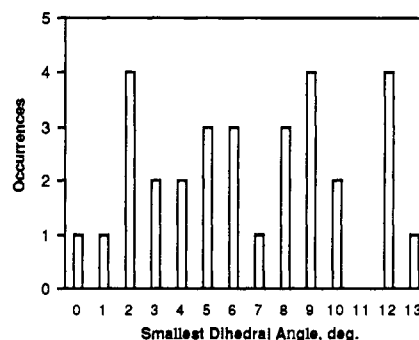


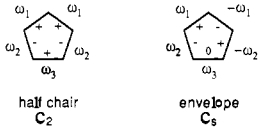
Figure 3. Torsion-angle distribution for the half chair/envelope family of cyclopentane conformations. Data was generated by searching with dihedral-angle criterion (6°). The dihedral angle shown in the plot is 0° for the envelope and 12° for the half chair. Energies of these randomly generated structures decrease regularly from 11.4057 kcal/mol at 0° to 11.4014 kcal/mol at 13°.

chirality check was not employed.

Butane. Butane has three local energy minima, two of which are symmetry related as mirror images.²⁶ The anti form is the global energy minimum and was therefore chosen as the starting geometry for our conformational searches. Three conformations were found by using the dihedral angle criterion, the anti and both gauche forms (Table I). Searching by conformational energy yielded one gauche and one anti form. Searches were run with refinement to achieve true local (or in the case of the anti form, global) minima.

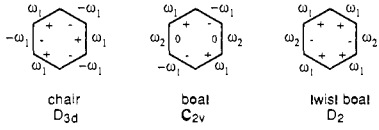
Cyclopentane. Cyclopentane (Table II) is known to freely pseudorotate³⁴ between the half chair (C₂) and envelope (C_s)

Table II. Data for Cyclopentane^a

search criterion	conformer (number found)				energy ^e
		ω_1^e	ω_2^e	ω_3^e	
dihedral ^b with refinement	half chair (10)	13.20 (0.13)	34.51 (0.08)	42.58 (0.01)	11.4013 (0.0000)
dihedral ^b no refinement	c (31)			6.56 (3.16)	11.4035 (0.0014)
energy no refinement ^d	c (7)			5.72 (2.06)	11.4102 (0.0073)
global	half chair	13.20 (0.05)	34.50 (0.03)	42.57	11.4013

^aEnergies in kilocalories/mole; angles in degrees. ^b6° tolerance criterion. ^cStructures vary from half-chair to envelope; only the smallest torsion angle (shown as ω_3 , corresponding to C_s) is well-defined. ^dNo new structures were obtained with energy with refinement. ^eMean deviations in parentheses.

Table III. Data for Cyclohexane^a

criterion	conformer family (number found)				energy ^b
		ω_1^b	ω_2^b		
dihedral (6°) with refinement	chair (2)	56.35 (0.01)		6.5509 (0)	
dihedral (6°) no refinement	twist boat (6)	30.82 (0.09)	63.98 (0.01)	11.9070 (0)	
	chair (2)	56.34 (0.26)		6.5539 (0.0030)	
energy (0.1) with refinement	twist boat (6)	30.80 (0.81)	63.94 (0.07)	11.9124 (0.0080)	
	boat (5)	52.39 (1.11)	1.75 (1.25)	13.0060 (0.0160)	
energy (0.1) no refinement	chair (1)	56.35 (0.01)		6.5509	
	twist boat (1)	30.82 (0.12)	64.00 (0.02)	11.9070	
global	chair (1)	56.35 (0.01)		6.5509	
	twist boat (1)	30.65 (0.67)	63.62 (0.58)	11.9142	
	boat (1)	52.22 (0.93)	1.66 (0.50)	13.0106	
	chair	56.35 (0.01)		6.5509	

^aEnergies in kilocalories/mole; angles in degrees. ^bMean deviations in parentheses.

Table IV. Data for Methylcyclohexane^a

criterion	chair		twist boat		twist boat		transition states
	equatorial	axial	pseudoequatorial	isoclinal	pseudoaxial		
energy with refinement	6.8902 [1]	8.6696 [1]	12.3107 [1]	12.7729 [1]	14.0665 [1]		
energy no refinement	6.8902 [1]	8.6907 [1]	12.3117 [1]	12.7736 [1]	14.0674 [1]		14.3938 ^b 13.6885 ^c
dihedral with refinement	6.8902 [1]	8.6697 [1]	12.3108 (0.0) [2]	12.7729 (0.0) [2]	14.0665 (0.0) [2]		
dihedral no refinement	6.8902 [1]	8.6901 [1]	12.3118 (0.0) [2]	12.7739 (0.0002) [2]	14.0670 (0.0002) [2]		13.6859 ^c 13.4378 ^d 18.3398 ^e
dihedral with refinement no chiral	6.8902 (0.0) [2]	8.6696 (0.0001) [2]	12.3108 (0.0) [4]	12.7729 (0.0) [4]	14.0665 (0.0) [4]		

^aEnergies in kilocalories/mole; angles in degrees; number of occurrences in brackets; mean deviations in parentheses. ^bPseudoaxial boat. ^cPseudoequatorial boat. ^dEquatorial boat. ^eHalf-chair transition state for twist boat-chair interconversion.

forms. Global minimization yielded the half-chair form as the most stable conformer. Ten symmetry-related structures were found by the dihedral angle criterion when refinement of the structures was employed. The corresponding search without refinement yielded a mixture of conformers that ranged from the half chair to the envelope; Figure 3 presents the overall distribution of conformers by their smallest dihedral angle. The random pattern displayed indirectly confirms the very flat potential energy profile for cyclopentane pseudorotation.³ Searching by conformational energy (with refinement) afforded only a single conformation. The corresponding search without refinement did not afford any new conformers until the conformational-energy tolerance was lowered to 0.001 kcal/mol, at which point the array of structures generated as similar to that found by the dihedral angle criterion (Figure 3). The small energy difference found between the C₂ and C_s forms (0.002 kcal/mol) is below the level of experimental uncertainty for molecular mechanics calculations,³ and no significance should be attached to their relative stabilities according to the MM2 force field.

Cyclohexane. Cyclohexane has two minimum-energy conformations, the rigid chair and the flexible twist boat; the boat form is generally accepted to be a transition state in the twist boat pseudorotation pathway.^{3,25,33} The results for this compound are summarized in Table III. Conformational searches with refinement afforded the chair and twist-boat conformations only. With the dihedral angle criterion six symmetry-related twist boats and two symmetry-related chairs were found. Searching by the energy criterion yielded a single chair and a single twist boat. The boat form was found only in the absence of refinement, a result that is in full accord with expectations for a transition state. Only five of the six possible (symmetry related) boats were found in the run reported in Table III. Structures other than energy minima are found much less efficiently by our program as a consequence of the optimization algorithm.

Methylcyclohexane. Methyl substitution on the cyclohexane ring increases the number of possible conformations. As shown in Table IV, the methyl group could occupy the axial or equatorial positions of the chair conformation and the pseudoaxial, pseudo-equatorial, or isoclinal positions of the twist boat. Finally, the methyl group in the boat conformation could be axial, equatorial, pseudoaxial, or pseudo-equatorial. The latter four conformers should all correspond to saddle points or higher order stationary points and are less likely to be located in a search. The other five conformations should all be accessible, however.

Each search performed with refinement afforded the five possible minimum-energy structures. Searching with the conformational energy criterion provided a single occurrence of each

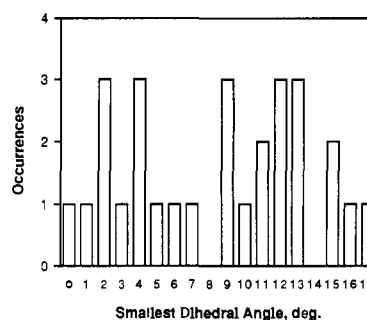


Figure 4. Torsion-angle distribution for the boat/twist boat family of cycloheptane conformations. Data was generated by searching with dihedral-angle criterion (12°). The dihedral angle shown in the plot is 0° for the boat and 15° for the twist boat. Energies of these randomly generated structures increase regularly from 17.4586 kcal/mol at 0° to 17.4603 kcal/mol at 17°.

of the five structures, but the mirror-image conformations of the twist boats were located when the dihedral angle criterion was employed. When the search was carried out without using the chirality check, two full sets of conformers were found. These two sets are related by inversion of configuration at the methyl-substituted carbon. This experiment shows the importance of the chirality check in appropriately substituted compounds. The relative energies found for the substituted twist boats are in agreement with Hendrickson's findings (pseudo-equatorial < isoclinal < pseudoaxial).³⁵ When the searches were carried out without refinement three of the boat forms were found together with a half chair corresponding to a transition state for interconversion between the chair and twist-boat conformations.^{3,33}

Cycloheptane. Cycloheptane exists in two families of conformations (boat and chair) that symmetrically interconvert.^{3,30,32,33,36,37} The boat and twist boat interconvert freely by pseudorotation, and they have approximately the same energy. The twist-chair forms interconvert less easily, and the symmetrical chair represents the barrier to the pseudorotatory process. The results for cycloheptane are summarized in Table V.

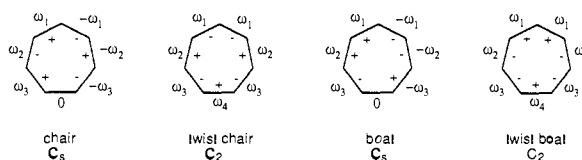
The searches performed with refinement (energy and dihedral) found two overall local minima; the boat and twist chair. Searching with the dihedral-angle criterion produced the expected symmetry-related conformers: 14 twist chairs and 14 boats, while energy searching found a single boat and a single twist chair. The earlier calculations of Hendrickson had afforded the twist boat as the local minimum with the boat as the interconversion bar-

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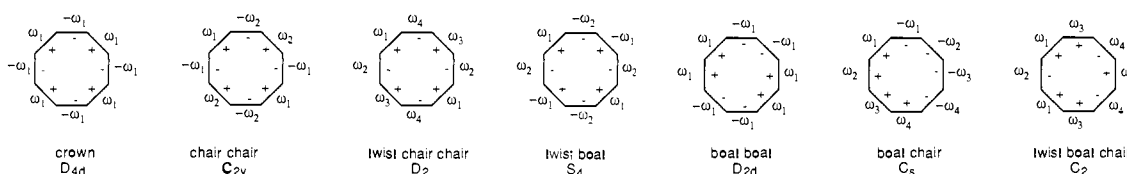
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Table V. Data for Cycloheptane^a

conformer family (number found)	ω_1^c	ω_2^c	ω_3^c	ω_4^c	energy ^c
chair (2)	64.82 (0.40)	84.94 (0.94)	66.90 (0.88)	1.26 (0.20)	15.3361 (0.0231)
twist chair (15)	38.88 (1.35)	87.52 (0.49)	72.66 (0.49)	55.12 (0.57)	14.3230 (0.0335)
twist chair (1)	38.99 (0.0)	87.73 (0.02)	72.53 (0.03)	54.81	14.3072
boat (1)	56.78 (0.06)	31.08 (0.06)	69.81 (0.06)	0.15	17.4585
twist boat (1)	45.06 (0.76)	65.86 (0.26)	15.38 (0.76)	70.40	17.4730
global	39.00 (0.02)	87.73 (0.02)	72.52 (0.02)	54.81	14.3072

^a Energies in kilocalories/mole; angles in degrees. ^b Structures vary from boat to the twist boat; only the smallest torsion angle is listed. ^c Mean deviations in parentheses.

Table VI. Data for Cyclooctane^a

conformer family (number found)	ω_1^d	ω_2^d	ω_3^d	ω_4^d	ω_5^d	energy ^d
boat chair (19)	64.91 (1.97)	43.47 (2.59)	101.69 (0.56)	68.12 (0.93)		19.4467 (0.0664)
twist chair chair (9)	64.43 (1.01)	84.60 (1.42)	111.11 (0.85)	85.82 (1.67)		20.3964 (0.0537)
chair chair (4)	78.88 (2.07)	96.05 (2.14)				20.5751
twist boat chair (16)	46.61 (1.37)	117.26 (1.36)	49.45 (1.13)	92.19 (0.55)	88.95 (0.86)	21.0915 (0.0458)
S ₄ (7)	36.06 (1.10)	65.10 (0.79)				22.5422 (0.0207)
boat boat (2)	51.56 (0.37)					22.9566 (0.0006)
boat chair (1)	64.82 (0.02)	43.58 (0.02)	101.72 (0.0)	67.72 (0.0)		19.4095
twist chair chair (1)	63.26 (0.0)	85.24 (0.0)	111.27 (0.01)	85.11 (0.0)		20.3750
twist boat chair (1)	48.21 (0.07)	117.39	48.84 (0.02)	92.08 (0.04)	89.19	21.0735
S ₄ (1)	36.49 (0.02)	64.80 (0.02)				22.5319
global	64.81 (0.01)	43.59 (0.0)	101.72 (0.02)	67.73 (0.02)		19.4095

^a Energies in kilocalories/mole; angles in degrees. ^b Energy search (0.01 tolerance) yielded the same seven conformational groups. ^c Dihedral search with refinement yielded the same four conformations. ^d Mean deviations in parentheses.

rier;^{30,32,33} Lifson found the reverse.³⁶ More recent studies indicate that the energy difference between the boat and twist boat is very small and that these forms freely interconvert by pseudorotation.³

Searches run by using the dihedral angle criterion without refinement located three structural classes: chair, twist chair, and boat/twist boat. Examination of the dihedral angles (Figure 4) reveals that the conformations for the last category range from the boat to twist-boat forms. As in the case of cyclopentane, this distribution results from the very flat potential surface for pseudorotation. The chair and twist-chair forms represent the remaining two energy classes. The chair is found to be 1.0 kcal/mol higher in energy than the twist chair and corresponds to the pseudorotatory barrier for interconversion.

Energy searching without refinement afforded similar results. With a conformational energy tolerance of 0.5 kcal/mol the chair and twist-chair forms can be located, but there can be no distinction between the boat and twist boat, so only one of them was found in any single run. When this tolerance was reduced to 0.001 kcal/mol, the search yielded a distribution of conformations (boat/twist boat) that was nearly the same as that shown in Figure 4.

Cyclooctane. Cyclooctane has generated much interest because of its large number of conformers and its inherent flexibility.^{3,27,31-33,38-42} Previous studies were performed almost exclusively

by systematic searches for possible conformations. The combined results from these earlier reports define seven low-energy conformations and three high-energy forms. We have performed various searches and have identified the seven low-energy forms (Table VI). Searching without refinement by either the dihedral angle or conformational-energy criterion yielded all seven low-energy forms. The three previously reported higher energy forms (boat, chair, and twist chair) were not found in any of the searches. Their absences strongly suggests that they are saddle points or higher order stationary points on the potential energy surface. The statistical probability of finding these forms is presumably very low.

The conformational-energy searches performed with refinement were repeated for a total of four runs, and the same four low-energy forms were obtained in each case: boat chair, twist chair

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chair, twist boat chair, and S_4 . The same results were obtained for the dihedral criterion with refinement. The remaining three low-energy forms (crown, chair chair, and boat boat) are each converted to one of these four structures upon minimization with refinement and suggests that they may not be minimum-energy structures. Their interconversion most likely occurs across families by free pseudorotation as suggested by Hendrickson.³³ In contrast to Hendrickson's model the twist boat chair was found to be a minimum-energy conformation. Although the boat chair form is the minimum for this conformational family as Hendrickson reported, the twist boat chair does not freely interconvert to the lower energy conformer. Anet has also reported these four structures as overall minima by utilizing a similar technique of refinement.⁴⁰

A previous report suggested that the crown, boat boat, and twist chair were all saddle points,³⁹ but this is in conflict with our results (and those of others).^{32,38-41} With the MM2 force field the twist chair chair is the lowest energy conformer for the crown family. The consistent finding of this conformer under conditions of refinement precludes it from being a saddle point.

Conclusions

The RIPS method constitutes a reliable technique for probing conformational space, locating local as well as global minima. Searches performed with refinement find true local minima, even on very flat energy surfaces, as illustrated by our results for cyclopentane and cycloheptane. The refinement procedure also provides a method for transition-state verification because even very small perturbations of the molecular geometry will result in optimization of a saddle-point structure to a new minimum-energy conformation.

Searching techniques without refinement are capable of locating most stationary points (minima and saddles) on the potential energy surface. This method of searching, under both dihedral angle and conformational energy constraints, affords a new method for mapping pathways of conformational interconversion. In many of the earlier studies, which were limited by the computing power available, geometric parameters were arbitrarily assigned and systematically varied to generate viable conformations. Results from such calculations depend on the investigator's intuition to choose the correct geometric parameters to vary. This requirement for prior knowledge of the conformational surface imposes an unacceptable constraint for investigation of complex systems.

As computing power has increased in availability, torsional-searching methods have become the standard approach for exploring conformational space.^{3,8,24} This technique relies on the assumption that the lowest energy pathway is accurately defined by the dihedral varied in the calculation, which is inaccurate.²⁴ Other dihedral angles may lag behind the angle being driven,^{3,24}

and transition states calculated by torsional searching may be distorted from the correct geometry. Moreover, the results of torsional searches have been found to depend on the choice of the torsional angle to be varied.⁴⁰

The RIPS method described in this report circumvents the pitfalls found in systematic search techniques and will converge to optima from randomly generated locations on the hypersurface. All degrees of freedom are varied when searching for stationary points, and structural perturbations are partitioned among all internal coordinates. We believe that this results in a very close approximation of the correct molecular geometry when the algorithm optimizes to a stationary point.

We have found that the RIPS method occasionally generates structures (usually of rather high energy) that do not correspond to any obvious energy minimum or transition state. These may be higher order stationary points on the MM2 hypersurface, or they may simply be artifacts. In any case they are easily recognized, usually having energies that are at least 10–20 kcal/mol higher than normal conformations and often exhibiting a single high-energy distortion such as an abnormally long bond length.

Advantages are offered by either of the RIPS methods for carrying out conformational searches, i.e., using the dihedral-angle criterion or the conformational-energy criterion. With dihedral constraints the search will locate all conformers having at least one dihedral outside the specified tolerance, even if some of them have nearly identical energies. This ensures that all conformations will be found. In cases where symmetry-equivalent conformations exist (e.g., as with the cycloalkanes studied here) data analysis is complicated by multiple occurrences of the same structure. However, most structures lack such symmetry, so this is not a significant disadvantage. Searching by the conformational-energy criterion will only locate structures having different energies on the potential surface. The data obtained by energy searching are more easily analyzed (and do not include symmetry-related structures), but this technique will fail to locate structures that have very similar energies. Overall the RIPS method offers a powerful approach to probing conformational space. The investigator requires no prior knowledge of the conformational behavior for the system that is to be studied, and by combining searches that utilize the dihedral-angle and conformational-energy criteria, both with and without refinement, a highly reliable conformational search can be conducted.⁴³

Registry No. Butane, 106-97-8; cyclopentane, 287-92-3; cyclohexane, 110-82-7; methyl cyclohexane, 108-87-2; cycloheptane, 291-64-5; cyclooctane, 292-64-8.

(43) Copies of the RIPS program will be made available to the chemical community in due course.