An Unbounded Systematic Search of Conformational Space

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A new method for searching internal coordinate conformational space systematically via a continuous-process procedure is described. Unlike previous systematic search methods, the new scheme generates torsionally remote conformers early in the search. It is also unbounded in that the extent of the search need not be specified at the outset. The search begins at low resolution (120° in torsion angle space) and then goes to higher and higher resolution as all points in space at a given resolution have been searched. The search may run without end or be terminated when new conformers cease to be found or when all space at some maximum allowable resolution has been explored. Conformational searches on several medium- and large-ring molecules using the new method are described and the results are compared with those from certain previously described search methods. It is found that the new method is significantly more efficient than previous procedures at finding all low energy conformers of organic molecules.

INTRODUCTION

Finding the populated, low energy structures of a molecule is a difficult problem when the molecule is conformationally flexible. While much progress has been made in methodology for finding such conformations of organic and biological molecules,[1] even simple structures having a dozen or so variable torsion angles still provide challenging problems.

Some of the best methods yet described use random searches in torsional or Cartesian space.[2] While apparently effective, such random methods are less than ideal solutions in that random searching is arguably the least efficient search strategy. In particular, the efficiency of such searches may be high in the beginning but degrades rapidly as the search proceeds: Late in the search, most of the time is spent rediscovering conformers previously found. Depending on the number of conformations actually present, finding the last 10% of all conformers may take considerably more time than finding the first 90%.

Systematic searches, on the other hand, maintain efficiency at the end of the search by avoiding regions of conformational space that have been explored previously.[2a,3] They have a further advantage in that they are deterministic and provide guaranteed sampling of all regions of space in a finite number of steps. Systematic searches are generally carried out first by generating a large number of starting geometries using all combinations of selected values for variable internal coordinates (e.g., torsion angles) and then energy minimizing these structures to yield the corresponding low energy final conformations. Such searches are batch processes in which the total number of search steps must be specified at the beginning of the search when the starting geometries are generated. Except for simple molecules, the number of steps that are necessary to find all conformations is unknown at the outset and may be so large that the energy minimization stage of the search becomes prohibitive. The problem is exacerbated by the necessity of using many values for each torsion angle since low energy conformations of flexible molecules commonly incorporate relatively high-energy torsional arrays (e.g., a syn-pentane fragment).[2a]

In our previous work on random searches,[2b] we found that conformational searches could be directed toward the low energy region of conformational space by using multiple low energy conformations as initial structures and varying in them only a fraction of the variable torsion angles. In this article, we describe a systematic variant of our internal coordinate Monte Carlo multiple minimum (MCMM) search. The new procedure was implemented as a continuous process search, which differs from previous systematic methods in that the extent of the search need not be specified at the outset. Instead, the search begins at low internal coordinate resolution (e.g., 120° in torsion angles), samples all points in conformational space, doubles the resolution, samples all new points, and so on. The process can continue without end and thus must eventually find all conformations in a finite number of search steps. The search also provides access to unusual values of internal coordinates by using systematic *variations* in internal coordinates as opposed to systematic *values* of internal coordinates. Thus it is a hybrid of our previously described systematic[3a] and random[2b] searches, which incorporates some of the best fea-

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tures of each. We term the new method "SUMM" for systematic, unbounded multiple minimum search. As we will demonstrate, it provides a more effective way to search conformational space than any other method we have tested.

METHOD

The search described here is a breadth-first search that begins at coarse torsion angle resolution (e.g., 120°). Since the volume of conformational space expands exponentially each time the resolution is increased, a search rarely samples all points in conformational space at the highest resolution achieved. Consequently we try to explore the more promising points early in the search of the conformational space at a given resolution.

Ideally, we would like to select points in conformational space that are low in energy and yield unique conformations upon energy minimization. Here, we use three tactics to accomplish these goals. To favor discovery of low energy conformers, we use the findings of our previous work.[2b] Thus we use low energy starting structures at each step (tactic 1) and vary in them fewer than the maximum number of variable torsion angles (tactic 2). To generate distinct conformations, we not only avoid replication of starting geometries systematically but also make each new starting geometry as different as possible from those previously explored (tactic 3).

In our discussions, we will use the following definitions: *initial structure*—the structure that is used to begin the conformational search, *starting structure*—a minimum energy conformation that is selected as a starting point for the next step of the conformational search, and *starting geometry*—a geometrically perturbed starting structure that is to be energy minimized to give a final, minimum energy conformation.

Systematic Searching of Conformational Space using the SUMM Method

The SUMM conformational search proceeds by (1) selection of a starting structure, (2) altering the torsional angles of the starting structure to produce a new starting geometry, (3) energy minimizing the starting geometry to produce a final, minimum energy conformation, (4) testing that final conformation for duplication with previously found conformations, and (5) go back to 1 as long as unique final conformations continue to be found. Steps 1, 3, and 4 have been described previously.[2b]

Let us first define all points in conformational space as an infinite, sequential list of integers N. We term each such integer N a "search step" and it represents a set of modifications (e.g., torsion angle rotations) which will be applied to the variable internal coordinates of some starting structure to give a new starting geometry for energy minimization. We order these points so that a simple incremental search through N will generate all points at a low resolution (e.g., 120° torsion angle resolution) followed by all points at double that resolution (60° torsion angle resolution) and so on, covering conformational space uniformly (tactic 3). We further order the list of points having the same resolution by the magnitude of the conformational change which is represented. Thus we place all possible single coordinate modifications before all possible pairs of coordinate modifications and so on. This organization favors the creation of new conformations which are low in energy (tactic 2).

The key procedure in the SUMM conformational search is generation of the torsion angle variations corresponding to search step N. The algorithm which converts N to a set of torsion angle rotations operates in four stages and the mathematical details are given in the Appendix. A descriptive account of the procedure follows for the N'th search step in which c is a simple index of operative resolution having values 1,2,3, etc.

Initialization

We first generate arrays $P(a,b,c)$ (the number of ways it is possible to alter a torsion angles out of a total of b variable torsions at resolution level c) and $Q(c)$ (the total number of ways it is possible to alter all torsion angles at resolution c). By comparing N with appropriate elements of these arrays, it is possible to the determination of the operative resolution level, the number of torsion angles to be varied and the particular torsional alterations to be made.

Stage 1. Determine the operative resolution level (C) at search step N and the search substep at that resolution (N_C). This is accomplished by comparing N with $Q(c)$. If N is greater than the number of ways it is possible to alter torsions at resolution level 1 ($Q(1)$), then the resolution must be 2 or more. If $Q(1) < N \leq Q(2)+Q(1)$, then the resolution level must be 2 (i.e., $C = 2$). By incrementing c to c' and comparing N with ΣQ, the operative resolution C will be found. By comparing C with the total number of torsional variations possible at each resolution level ($Q(c)$, c = 1,2, ...), we can evaluate N_C, which is one more than the number of search steps already made at the resolution C.

Stage 2. Determine the number of torsions to be altered (A) and the search substep at resolution C with A torsions (N_{AC}). The value of A can be found by comparing N_C with the number of ways it is possible to alter a given number (a) of variable torsions ($P(a,B,C)$) where B is the total number of variable

torsions. Suppose the minimum number of torsion angles that can be altered is one ($A = 1$). There are $P(1,B,C)$ ways of altering one torsion out of B at resolution C, so $A = 1$ if $N_C \leq P(1,B,C)$. Similarly $A = 2$ if $P(1,B,C) < N_C \leq P(1,B,C)+P(2,B,C)$, and so on. By analogy with the way N_C was found, we evaluate N_{AC} which is N_C less the number of ways to alter fewer than A torsions out of a maximum of B torsions at resolution C.

Stage 3. Permute N_{AC} to N_{CA}. At this stage, N_{AC} corresponds to a number which could be deciphered to give a set of A torsional alterations. However, because of the way in which N_{AC} is constructed, adjacent search steps (N_{AC} and $N'_{AC} = N_{AC} + 1$) would represent points quite close to one another in conformational space. For example, adjacent search steps for 1-decanol could represent rotations of torsions corresponding to 0,0,0,0,0,0,0,0,120 and 0,0,0,0,0,0,0,0,240 degrees (0 = no rotation). To make adjacent search steps generate changes in remote parts of the structure, we write N_{AC} in binary, reverse the binary digits and interpret as the base 10 number N_{CA}. This operation effectively mixes the torsion angles to be varied so that adjacent N_{AC}'s will generate remote points in conformational space.

Stage 4. Decipher N_{CA} as a series of torsion angle variations. At this stage, N_{CA} is a unique number which represents the desired A torsional variations. One way to decipher N_{CA} is to make a list of integers from 1 to the total number of ways it is possible to alter 1 through A torsions out of all B variable torsions at resolution level C. Each of these integers is a possible value for N_{CA}. If we write these integers in an arithmetic base equal to the number of possible values for a torsion at resolution C, each digit of these numbers can represent an alteration for a particular torsion angle. When $C = 1$ (120° resolution) for example, the base would be 3 and the digits 0, 1 and 2 would correspond to torsional rotations of 0, 120, and 240°. If we now remove all entries in the list not having exactly A nonzero digits, then the N_{CA}'th remaining entry will define the rotations required. A more efficient method for accomplishing the same goal is outlined in the Appendix.

The search itself is carried out by choosing the i'th starting structure using the uniform-usage protocol,[2b] incrementing its particular search step ($N_i = N_i + 1$) and then interpreting N_i as a series of torsional rotations as described above. The torsional rotations are applied to the starting structure to give a new starting geometry, which is energy minimized. The final structure is then compared with previously found conformations for duplication. The next search step follows by again choosing a starting geometry (j), incrementing its particular search step (N_j), and so on. The search is continued as long as resources permit or until unique conformations cease to be found.

Torsional Memory

While the systematic search sequence with a single starting structure will not retrace its steps, multiple starting structures make redundant coverage possible because similar starting geometries may be generated from different starting structures. This problem can be avoided by checking each new starting geometry against all previous starting geometries and starting structures. In the current method, we do this by storing and testing values of variable torsional angles and use the term *torsional memory* to describe this procedure. Using torsional memory, starting geometries are rejected by the torsional memory test if a comparison with stored torsion angles shows no difference of more than half the operative torsion angle resolution.

A refinement was added to the simple torsional memory scheme for cases in which starting geometries are very different from the final structures formed from them by energy minimization. In such instances, the conformational surface close to the starting geometry would probably not have been carefully investigated, since the energy minimization algorithm moves the conformation to a new area of the potential surface. For this reason we check that each final structure is similar to the starting geometry that generated it. A structure and the starting geometry are considered to be similar if no corresponding torsional angles differ by more than 120°. If the structures are not similar, then only the final structure after energy minimization is stored in the torsional memory.

In a conformational search of a large or flexible molecule, the torsional memory requires a large amount of disk space. The maximum size of the torsional memory in our computer program is currently set to allow 10,000 structures to be stored. If a search generates more structures than this, then the subsequent structures are not added to the torsional memory; although, all new structures are still checked against the first-stored 10,000 sets of torsion angles.

Preoptimization of cyclic Structures

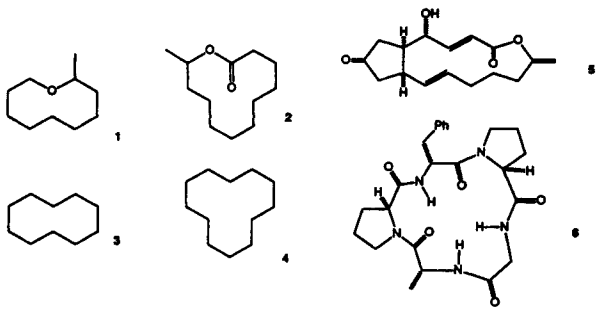
If the structure being investigated contains a ring, then the energy minimization phase of the search may begin with a structure having one abnormally long ring closure bond. Since the corresponding stretch derivatives would be large, the bond length would be corrected rapidly but likely at the expense of distorting significantly other parts of the structure. Such distortion could involve major changes in nearby torsion angles and thus undermine our systematic coverage of torsion angle space. Therefore, our search might be improved by preoptimizing each structure in such a way that the ring closure bond length is adjusted by a method that delocalized the associated

geometry modifications over all variable torsion angles.

To this end, we wrote a simple preoptimization routine which operates by sequentially altering each torsion angle that affects one, and only one, ring closure distance. The routine first uses analytical geometry to calculate how much adjustment is required to bring the ends of the ring as close as possible to the optimal ring closure distance, keeping the rest of the molecule rigid. The torsion angle is then adjusted in this direction, but generally by no more than one eighth of the current resolution (e.g., 15° at 120° initial resolution). If the angle being optimized is one of those which had been perturbed to produce this new starting geometry, then we allowed it to be altered by as much as the current resolution. After altering each ring torsion angle, ring closures are much closer to their optimal distance. This routine, in combination with the torsional memory, further improved the conformational searches.

RESULTS

To test the effectiveness of the new method at finding all low energy conformations of simple molecules, we carried out a series of conformational searches on structures **1–6.** We use the AMBER united atom representation of these molecules to speed the searches.[4]



Our initial studies were carried out on the 10-membered ether **1.** This is a simple molecule but its asymmetry makes it rich in low energy minima in comparison with cyclodecane **3.** The fully symmetrical **3** has only 12 distinct minima within the lowest 50 kJ/mol while **1** has 175.

Effect of the New Procedures on Conformatinal Search Results

To establish the effectiveness of the torsional memory and the preoptimization schemes described in the Methods section, we carried out a series of 1000-step conformational searches both with and without these procedures. In the context of this work, we define a step as the generation and minimization of one starting geometry. Since the searches depend somewhat upon the initial structure chosen, we conducted the systematic searches in triplicate beginning with three different initial structures. The results are given in Table I and are compared with averages of four independent MCMM Monte Carlo torsion angle searches[2b] from the same three starting structures.

As shown in the table, the MCMM Monte Carlo searches found an average of 163, or 93%, of the 175 total minima of **1** in the 1000-step searches. In comparison, the simple systematic search method described above did less well, finding only 91% of the minima in the same number of steps. The poor performance of the systematic search follows from the way it operates. In particular, the search systematically avoids regions of conformational space, but only with respect to the starting structure with which the search step begins. Thus different starting structures occasionally yield similar starting geometries which would not be detected as potential duplicates by the systematic scheme alone. To identify such similar starting geometries, we use the internal coordinate checking mechanism described above and

Table I. Comparison of 1000-step Monte Carlo and here-described systematic conformational searches of cyclic ether **1.**

Search method	Number of unique minima found within 50 kJ/mol of the global minimum[a]	CPU time[b] (minutes)
Monte Carlo (MCMM)[2b]	161,[c,d] 164,[c,e] 163[c,f] (average 163, 93%)	59
Systematic (see text)	159,[d] 157,[e] 159[f] (average 159, 91%)	61
Systematic + torsional memory	168,[d] 169,[e] 168[f] (average 168, 96%)	69
Systematic + torsional memory + preoptimization	173,[d] 173,[e] 174[f] (average 173, 99%)	62

[a]Total number of known minima of **1** with the AMBER force field is 175 within the first 50 kJ/mol.
[b]Measured on a single processor of an Apollo DN 10000 workstation.
[c]Average of four runs using different random number sequences.
[d]Starting from the global minimum.
[e]Starting from the fifth structure energetically above the global minimum.
[f]Starting from the tenth structure energetically above the global minimum.

Table II. Number of search steps necessary to find all known low energy conformations of molecules **1-4.**

Molecule	Method	Number of minima found	Number of steps required[a]
1[b]	MCMM	175	3161[d]
	SUMM	175	1481, 1313, 1232 (av. 1342)[f]
2[c]	MCMM	157	>5411[d,e]
	SUMM	157	3535, 3401, 3395 (av. 3444)[f]
3[b]	MCMM	12	81[d]
	SUMM	12	16, 27, 34 (av. 26)[f]
4[b]	MCMM	82	1943[d]
	SUMM	82	1525, 1280, 1281 (av. 1362)[f]

[a]Number of starting geometry energy minimizations.
[b]Conformations within lowest 50 kJ/mol.
[c]Conformations within lowest 25 kJ/mol.
[d]Average of four independent runs using different random number sequences.
[e]One MCMM search failed to find all minima in 10000 steps.
[f]Results from three different starting geometries.

involving what we termed "torsional memory." Torsional memory allows rejection of new starting geometries which are similar to previously used starting geometries prior to the time-consuming energy minimization process.

Using torsional memory enhances the effectiveness of the search substantially. However, the results are still only a little better than those of the Monte Carlo searches. Why? It is likely that the two methods perform comparably well for different reasons. The systematic method avoids redundant coverage of conformational space but does so by favoring conformations which differ by 120° torsion angle increments (at least early in the search). It is well known that macrocycles in general and medium rings in particular commonly incorporate torsion angles far from their local energetic minima. The Monte Carlo method generates starting geometries having such nonstandard torsion angles but incorporates no way of avoiding starting geometries which were previously generated.

The final modification to the systematic search preoptimizes closure bond lengths prior to energy minimization. Such preoptimization favors production of minima which are closely related to starting geometries. These adjustments also move torsion angles away from standard values and may also provide enough conformational change that the structure may be eliminated by torsional memory. As shown in Table I, using preoptimization with torsional memory significantly improves search performance and allows 99% of the known minima of **1** to be found in 1000 steps.

Table I also indicates that the time necessary for generating a starting geometry is short relative to that necessary for energy minimization. Even with torsional memory testing and simple internal coordinate preoptimization, only 5–6% of total CPU time was used in creating starting geometries in our systematic search.

Finding all low Energy Conformations of Simple Molecules

In the tests described above, the systematic procedure using ring closure preoptimization and torsional memory performed well at finding the low energy conformations of **1.** We expect, however, that the systematic method would have a greater advantage when the objective is *all* low energy conformations of a molecule.

Both systematic and random methods operate with similar efficiency early in the search when much conformational space is unexplored. However, finding the last few unique conformations is the really hard part of a conformational search. As a random search proceeds, it spends a greater and greater proportion of its time generating structures in previously explored regions of space. Thus its efficiency degrades as the search nears completion. In contrast, systematic methods avoid reexploration of conformational space and should have an advantage in

Table III. Number of conformations of **5** and **6** found in a fixed number of search steps.

Molecule	Method	Number of search steps[a]	Number of conformations found
Oxobrefeldin **5**[b]	MCMM	5000	226, 236, 231, 233 (av. 231)[d]
	SUMM	5000	237
Peptide **6**[c]	MCMM	2000	189, 190, 105, 187 (av. 165)[d]
	SUMM	2000	260

[a]Number of energy minimizations.
[b]Conformations within lowest 50 kJ/mol.
[c]Conformations within lowest 25 kJ/mol.
[d]Average of four independent runs using different random number sequences.

completing a conformational search, i.e., in finding all conformations.

To compare the effectiveness of our random (MCMM) and systematic (SUMM) search methods at finding all[5] low energy conformations of simple molecules, we carried out a series of lengthy conformational searches on structures **1–4.** All searches were carried out with the usage-directed structure selection scheme[2b] in which all conformations found within the operative energetic bounds served as starting structures an equal number of times. The results are given in Table II. It may be seen that the systematic SUMM search outperforms average results of the random MCMM method in all of the trials. In a few individual MCMM searches, all conformations were found in roughly the same number of steps as required by the SUMM procedure. In other searches, 3–4 times as many MCMM steps as SUMM steps were required.

With still larger molecules, finding all minima is a lengthy process. Consequently, we asked which of the two methods, the random MCMM or the systematic SUMM, would find more conformations of a flexible structure within a short, fixed-length search. Using oxobrefeldin **5** and cyclic pentapeptide **6,** we carried out a series of 5000- and 2000-step searches and give the number of unique, low-energy conformations found in Table III. While the oxobrefeldin searches gave similar results with both methods, the peptide search was significantly better using the systematic search. Since the systematic method has a significant advantage only in the latter part of a search, we would expect that the systematic SUMM results would be still better if the searches were carried farther toward completion.

The lowest energy conformations of **5** and **6** found were those described previously based on experimental work.[6,7] All of the searches using either method found the same global minima.

CONCLUSION

We have described a method by which two of the main advantages of random internal coordinate conformation search can be incorporated into a systematic search with improved convergence characteristics. These advantages are: (1) an unbounded, continuous search process in which the extent of the search need not be specified at the outset, and (2) a search method which provides access to torsion angles having other than idealized values. The method was further defined so that the widely separated regions of conformational space are explored first at low resolution and then at higher and higher resolution as the search proceeds. We find that the method (entitled the SUMM method) is indeed more effective at finding all or nearly all low energy conformations of simple flexible molecules that the best previously described method (the MCMM method[2a,b]). In the tests performed, the SUMM search found all conformations of the medium ring compounds **1–4** in half to two-thirds of the time required by the MCMM search. In only one case, the partial search of oxobrefeldin **5,** did the SUMM approach show no advantage over the MCMM method. In all other cases, the SUMM search performed significantly better.

In summary, the SUMM search is the method of choice for conformational searching of simple molecules. With highly flexible molecules for which converged searches are not feasible, previously described methods seem to perform just as well provided that jumps between widely separated regions of conformational space are somehow incorporated into the search procedure. Most methods except molecular dynamics would appear to fulfill this requirement.[8]

APPENDIX: INTERPRETING SEARCH STEP *N* AS A CONFORMATIONAL SEARCH STARTING GEOMETRY

Start with a molecule having B torsion angles which are to be varied at initial resolution corresponding to R. R is defined as the number of ways it is possible to alter a torsion angle. Starting at 120° torsion angle resolution, R would be 2 (360°/120° − 1 = 2). We define c as the resolution level and give it as an integer which starts at 1 for the initial resolution (e.g., 120°). After some number of steps ($Q(1)$ below) in a conformational search, all points at the initial resolution level $c = 1$ (120°) have been examined. At that point the resolution level c is incremented to 2 and the torsion angle resolution is doubled (e.g., to 60°). $M(c)$ is the number of possible ways to alter a torsion angle at resolution level c given an initial resolution R is

$$M(c) = (2^{c-1}(R + 1)) - 1$$

Before the actual search begins, we create two arrays, $P(a,B,c)$ and $Q(c)$. The elements of the first array, $P(a,b,c)$, are the number of ways it is possible to alter a torsion angles out of the total of b at resolution level c. The elements $P(a,B,c)$ may be easily calculated when $a = 1$ and when $a = B$ as shown below. The remaining elements may be found by use of a recurrence relation

$$P(1,b,c) = b\,M(c) \qquad P(b,b,c) = M(c)^b$$

$$P(a + 1, b + 1, c) = M(c)P(a,b,c) + P(a + 1, b,c)$$

In practice, $P(a,B,c)$ and $Q(c)$ need only be evaluated for $c = 1$ and $c = 2$ since the number of points in conformational space at resolution $c \geq 2$ is very large.

The second array, $Q(c)$, has elements which are the totals of the number of ways it is possible to alter B torsion angles at resolution c. Minimum and maximum below refer to the minimum (typically 1)

and the maximum (typically B) numbers of torsion angles to be altered simultaneously.

$$Q(c) = \sum_{a=\text{minimum}}^{\text{maximum}} P(a,B,c)$$

Given $P(a,b,c)$, $Q(c)$, and search step N, we interpret N as a set of torsion angle variations which are applied to a starting structure to give a new starting geometry using the following four stage procedure.

Stage 1

Determine C, the resolution level of search at the current search step N. This can be accomplished by comparing N with the number of possible ways ($Q(c)$) to alter torsion angles at any given c. The current resolution level C will be the largest c such that

$$\sum_{i=1}^{c} Q(i) < N$$

Also determine N_C, the search step at the current resolution C. N_C is N less the number of steps at all previous resolutions and thus is given by

$$N_C = N - \sum_{i=1}^{C-1} Q(i)$$

Stage 2

Similarly determine A, the number of torsion angles to be altered at step N. This can be accomplished by comparing N_C with the number of possible ways ($P(a,B,C)$) to alter torsion angles a at a time. Thus A will be the largest integer a such that

$$\sum_{i=\text{minimum}}^{a-1} P(i,B,C) < N_C$$

Also determine N_{AC}, the search for A torsion angles at resolution C. N_{AC} is N_C less the number of all possible ways to alter fewer than A torsion angles and thus is given by

$$N_{AC} = N_C - \sum_{i=\text{minimum}}^{A-1} P(i,B,C)$$

Stage 3

Permute N_{AC} to N_{CA} so that sequential search steps do not produce starting geometries that are adjacent in conformational space. We accomplish this by writing N_{AC} in binary and reversing the order of the digits, to give a new number N_{CA}. Neither N_{AC} nor N_{CA} may be greater than $P(A,B,C)$, so if N_{CA} is too large, N_{AC} is used instead. An example is given below for $P(A,B,C) = 8$.

N_{AC}	Binary	Reversed binary	N_{CA}	
1	0001	1000	8	
2	0010	0100	4	
3	0011	1100	3	(12)
4	0100	0010	2	
5	0101	1010	5	(10)
6	0110	0110	6	
7	0111	1110	7	(14)
8	1000	0001	1	

Stage 4

N_{CA} is now deciphered to give the corresponding torsion angle variations. The number of ways to alter A torsion angles out of a total of B at resolution level C is $P(A,B,C)$. We consider each torsion angle in turn. For the first torsion, no alteration is necessary if $N_{CA} \leq P(A,B-1,C)$. Otherwise, the first torsional rotation is given by an integer given by

$$T = 1 + \text{INT}[(N_{CA} - P(A,B-1,C) - 1)/P(A-1,B-1,C)]$$

Integer T will have a value between 1 and $M(C)$. The angular rotation for torsion angle is the product of T and the angular resolution (e.g., 120° when C = 1). Next the second torsion is treated similarly after we modify A, B and N_{CA} to A', B', and N_{CA}' to allow for the previous processing of the first angle. If we varied the first torsion, then we have $A - 1$ angles left to move ($A' = A - 1$). There are $B - 1$ torsion angles left that we must vary ($B' = B - 1$). If we did not move the first torsion, $N_{CA'} = N_{CA}$. Else

$$N_{CA'} = N_{CA} - T\,P(A-1,B-1,C)$$

The movement of the second torsion is now found as described above but using A', B', and $N_{CA'}$, and so on until all B torsion angles have been found.

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$C(sp^3)$—$C(sp^2)$	k_o = *317*	l_o = 1.525 Å
O=C	k_o = 570	l_o = 1.200 Å
O—$C(sp^2)$	k_o = 450	l_o = 1.330 Å
O—$C(sp^3)$	k_o = 320	l_o = 1.425 Å
O=C—O	k_o = 80	θ_o = 124°
$C(sp^2)$—O—$C(sp^3)$	k_o = 85	θ_o = 112°

O—C(sp^2)—C(sp^3)	k_o = 80	θ_o = 109°
O=C—C(sp^3)	k_o = 80	θ_o = 125°
C(sp^3)—C(sp^2)—O—C(sp^3)	$V1$ = 0.25	$V2$ = 2.75
O=C—O—C(sp^3)	$V1$ = −0.25	$V2$ = 2.75
C(sp^2)—O—C(sp^3)—C(sp^3)	$V1$ = −0.75	$V3$ = −0.75
C(sp^3)—C(sp^3)—C=O	$V3$ = −0.03	
C(sp^3)—C9sp^3)—C(sp^2)—O	$V3$ = 0.03	

5. We cannot prove that all conformations within the given energetic bounds of the target structures have been found by the searches described. However, a minimum of 10 lengthy searches using different methods found each conformer five or more times.
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