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Sampling conformational hyperspace: Techniques for improving completeness

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Summary

Three new strategies for sampling the conformation space accessible to a series of structurally diverse, flexible molecules are defined and compared to samples obtained using a fixed-grid torsion angle sampling strategy. A set of 28 potent inhibitors of angiotensin converting enzyme selected by Mayer et al. [J. Comput.-Aided Mol. Design, 1 (1987) 3] and the unrestricted active-site model proposed by Waller et al. [to be published] are used to produce a realistic experimental setting. We modified our Constrained Search algorithm [Dammkoehler et al., J. Comput.-Aided Mol. Design, 3 (1989) 3] to support these new sampling strategies, performing a series of 64 simulations (search experiments) and generating a large set of sterically allowed conformations. In each experiment, we systematically vary the internal torsion angles in each molecule using one of the sampling strategies. The common orientations of preselected functional groups thought to represent those dominating the interaction with the enzyme and presented by the set of molecules are classified and recorded for each experiment. Pairwise distances between groups are used to characterize the geometry of the common orientations. The results of each experiment, represented by a set of distance values, are compared and combined to evaluate the completeness of the conformational sampling. While no pure strategy or single search experiment was found to be adequate to fully explore the set of common sterically allowed conformations, a new sampling technique, called adaptive radial sampling, is shown to be significantly more complete than the commonly used fixed grid sampling.

Introduction

Molecular recognition is a central problem in biological science and forms the basis of specificity seen in drug–receptor, hormone–receptor, antigen–antibody and substrate–enzyme interactions. A basic concept is that of the complementarity of the shape and electrostatics of a small molecule and an active site. With rigid molecules, traditional structure–activity relationships (SARs) can determine the functional groups necessary for activity and their relative orientation at the receptor site (i.e., the pharmacophore). For flexible molecules, the situation becomes inherently more complex. Functional groups can no longer be changed with impunity due to their potential effects on conformational flexibility. Changes in steric interactions can alter the conformational possibilities available to the molecules, while changes in other properties (charge, hydrophobicity) can modify the population distribution of conformers made available to and recognized by the receptor.

If one assumes that a common binding mode exists for two or more flexible compounds, then one can use the computer to verify the assumption of geometric complementarity of corresponding functional groups. There are two distinct approaches to this problem. The first focuses on the existence issue, i.e., the question whether or not there is a minimum energy conformation of each of the molecules under consideration that will place the designated functional groups in a similar orientation. The second approach attempts to systematically sample the infinite set of conformations accessible to each of the compounds in order to determine common orientations or

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spatial patterns of functional groups presented by the set of active analogs. In this paper, we concentrate on the latter, the Active Analog Approach [6], and on recently developed techniques for more efficient sampling of conformational hyperspace.

In the Active Analog Approach [6], as in any other empirical study, there are two types of errors that can occur. The first is an error of omission. If important samples are inadvertently omitted from the data set, the results cannot be reliable. A second type of error, a classification error, occurs if the experiment does not correctly distinguish between truly different sample values or fails to recognize equal-valued samples. To us, the need to minimize these errors is the essential issue in the design of an effective conformational sampling experiment. In this paper, we focus on the appropriate selection of two of the three types of adjustable parameters that define an experiment (e.g., the torsional angle increment value and the classification, or geometric similarity, parameter). The third type of parameter is a set of van der Waals scale factors used to allow additional conformational flexibility, naturally arising from bond length and bond angle variations. Because we assume a fixed valence geometry in order to minimize the number of internal degrees of conformational freedom, bond length and bond angle variations are not treated explicitly in the Active Analog Approach [6], but are accommodated by appropriate calibration of the van der Waals scale factors [4].

Methods

We use the computer and sampling strategies to test the validity of the medicinal chemist's structural hypotheses regarding recognition and binding by identifying the common orientations (geometries) of specified functional groups in a series of bioactive compounds. To expedite the evaluation of those hypotheses, we have developed a very efficient build-up procedure [5] to minimize the time cost of generating sterically allowed complete conformations consisting of sterically allowed partial conformations. For each sterically allowed complete conformation of each molecule, the set of distances between all pairs of functional groups or pharmacophore reference points is calculated. The collection of all such points, each of which represents a unique pharmacophoric pattern, is stored in an orientation (or information) map, built and maintained by the computer program. If all molecules share the same binding mode, the common pharmacophoric pattern must be contained in the logical intersection of the information maps of the set of analogs. An efficient algorithm (Constrained Search) and a program for finding these common patterns have been previously described [3].

In Constrained Search, active-site geometries are represented by points in a multidimensional distance space, whose orthogonal basis vectors are the pairwise distances between the essential functional groups as designated by the user. The coordinates of a point in that space characterize the geometry of one orientation of the functional groups. We obtain a discrete sample of distance space by partitioning the enclosed volume into small hypercubes with equal and fixed edge length. We refer to this user-specified hypercube edge length as the classification parameter. Two points (geometries) are considered to be the same if they are both contained in the same hypercube partition of distance space. Clearly, this assumption is valid when the hypercube edge length is infinitesimal. As the value of the edge length increases, the probability of a classification error increases as well.

The most common methods of sampling conformation space are called grid searches. Most often, a single integer torsion angle increment is used to define (a priori) a regular grid of sample points in a multidimensional torsion angle space. In the original versions of Constrained Search [3] and its predecessor Systematic Search [6], the conformation space accessible to each molecule is sampled by generating conformations corresponding to discrete points in this space. Both algorithms generate the coordinates of all atoms of each molecule using torsion angle values corresponding to each grid point. The interatomic distances between each pair of nonbonded atoms in each conformation are calculated and checked for steric feasibility using minimum van der Waals constraint values. If a conformation is sterically allowed, the distances between all pairs of pharmacophore reference points (particular atoms associated with each functional group) completely characterize a possible geometry of a pharmacophore or active-site model.

Radial sampling is proposed as an alternative to the uniform torsion angle sampling strategy defined above. In radial sampling, torsion angle increments for each rotation are calculated by dividing the circumference of the circle of rotation of a key atom, V, into arcs of equal length. One key atom is specified for each torsional rotation, as described below. The arc length is a user-specified value that determines the maximum distance that the key atom can move in each rotational step. Torsion angle values are generated and used to control the generation of conformers during the search. The torsion angle increment is determined as follows:

$$\text{torsion angle increment} = 360.0 * \text{arc} \frac{\text{length}}{\text{circumference}} \quad (1)$$

The resulting angles are typically real values, represented internally as floating point numbers, and unique to each rotatable bond.

To implement radial sampling, we require that each variable torsion angle be specified by four atoms (U, S, R, V) and the planes USR and SRV, as shown in Fig. 1.

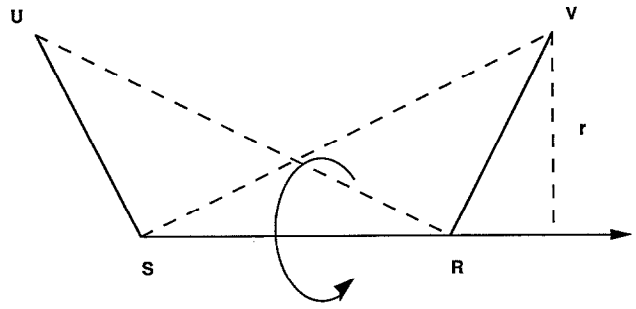

Fig. 1. Selection of key atoms.

The axis of rotation is determined by the coordinates of atoms S and R. The bond between S and R is referred to as a rotatable bond, and S and R are called the source and reference atoms, respectively. In the simplest case, U and V are atoms covalently bound to S and R, respectively. The positions of atoms U, S and R remain constant during each rotational step, while V moves clockwise around the axis of rotation when viewed from S to R. The perpendicular distance from V to the line containing SR is the value of the radius of the circle of rotation and determines the circumference referred to in Eq. 1. The key atom V can be any atom other than S that is covalently bonded to R or any other nonbonded atom that is connected to R by a sequence of nonrotatable bonds.

The following criteria are used to select key atoms for each radially sampled torsion angle. Let P be the nonempty set of bonded and nonbonded atoms from which V is to be selected. Additionally, assume that each atom in the set P has a type and a unique identification number. Basic types include pharmacophore reference atoms, reference atoms for rotational axes and general atoms. The identification numbers indicate the relative importance of each atom of each type and may be assigned by the investigator prior to each search. If P contains one or more pharmacophore atoms, the lowest numbered pharmacophore atom is selected as V. Otherwise, if P contains one or more atoms that are reference atoms for other rotations, the reference atom of the lowest numbered rotation is selected. Finally, if P does not contain pharmacophore or reference atoms, the lowest numbered atom contained in P is selected as the key atom.

Adaptive sampling is a new strategy, which can be used in conjunction with uniform angle or radial sampling. The objective is to minimize the possibility that important sterically allowed conformations are undetected during a search. Adaptive sampling uses a fixed angle increment as a basis for spacing sample points, but augments the fixed sample with points in small ranges between sample points that might otherwise be unsampled. Prior to each rotation we find the set of torsion ranges where acceptable conformations exist. This information is obtained by analytically solving the set of constraint equations defining all critical distances (van der Waals constraint and pharmacophore distances) between nonbonded atom pairs, and then finding the end points of the angle ranges containing conformations that satisfy all those distance constraints. Torsion angle values from each of these ranges are then selected in order to generate additional probes of conformational hyperspace. The details of the computation are shown below.

We have previously shown [3] that the square of the distance between a fixed atom i and an atom j rotating around a fixed axis as a function of a single torsional variable ω may be expressed by a simple equation with scalar coefficients:

$$d_{ij}^2(\omega) = a + b\cos\omega + c\sin\omega \tag{2}$$

We have also shown that there exists a straightforward transformation of variables, which converts such equations to a quadratic form:

$$d_{ij}^2(x) = (d_1x^2 + d_2x + d_3)/(1 + x^2) \tag{3}$$

where x is the tangent of $\omega/2$, and

$$\sin\omega = 2x/(1 + x^2) \tag{4}$$

$$\cos\omega = (1 - x^2)/(1 + x^2) \tag{5}$$

We note, as did Bruccoleri and Karplus [7], that the choice of ω for a general torsion angle conflicts with the more common use of ω as the peptide torsion angle, but we prefer to maintain consistency with the notation used by Gō and Scheraga [8].

We refer to any relation like Eq. 2 as a distance constraint equation. If the distance between a pair of atoms is a known quantity, i.e., a fixed bond length or invariant triagonal distance implied by a fixed bond angle, or a minimum allowable van der Waals distance, the equation can be simplified algebraically and solved using the quadratic formula to find the two values of the torsion variable ω that satisfy the constraint. Those values are the end points of two ranges. For energetic constraints, one range corresponds to an infinite set of sterically allowed conformations. The other range describes the infinite set of conformations that violate the particular van der Waals minimum-contact distances. The intersection of the ranges containing the allowed conformations for all nonbonded atom pairs produces a set of disjoint ranges that characterizes the accessible conformation space. We refer to the case where a set of disjoint ranges is encountered as a fragmentation of the torsion angle range, and have experimentally determined that fragmentation occurs with high frequency during a search. We also found that the separation of ranges is essentially random. This is characteristic of a physical situation where the search is attempting to dock a molecular fragment on an irregular surface

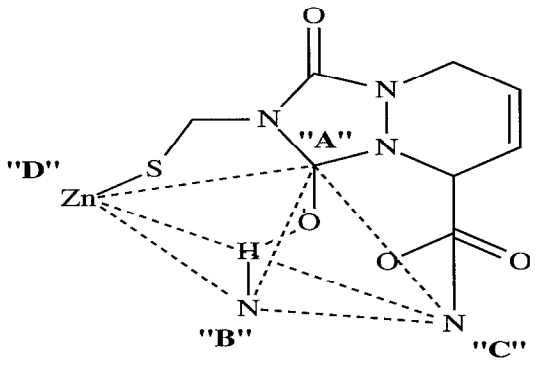

Fig. 2. The unrestricted active-site model.

formed by the prior assembly of other irregularly shaped fragments.

The case where the intersection of ranges produces a single, small range of valid angle values is called a constriction. Constriction is characteristic of the physical situation encountered when a geometric constraint with both minimum and maximum values is used to guarantee that the conformations satisfy the requirements of ring closure or other experimentally derived (NMR or NOE) constraints.

If the intersection of the analytically determined torsion angle ranges is not empty, the next step is to select the placement of sample points in each range. The number and size of the ranges are highly variable. A typical set of van der Waals constraint equations may yield several 20°–30° ranges. Ring closure constraints often imply several ranges of 0°–4° in length. Additional pharmacophore constraints routinely yield even smaller ranges of allowed angles. The combination of all such ranges produces a detailed picture of the opportunities for incrementally building larger structures guaranteed to meet all relevant constraints.

When a large range exists relative to the fixed grid interval, the body of the range is sampled at the regular fixed sample points. The edges of the ranges are further examined to see if a sample at half the fixed interval can be inserted. This is known as 'fixed' mode adaptive sampling. In effect, this provides a sampling at twice the rate of the standard increment. Additionally, if the range is otherwise unsampled, it is sampled at its midpoint. This is known as 'modified' adaptive sampling. Other strategies for sample placement have been examined; however, they are primarily Monte Carlo sampling techniques, and are not considered here.

Experimental design

The unrestricted active-site model proposed by Waller et al. [2] was used in our sampling studies. The enzyme zinc atom, an -NH group and the N^+ of a putative arginine residue are connected to the appropriately ionized inhibitor by dummy bonds and represented as formal atoms. Four points from the augmented structures were selected as reference points. Point 'A' is the carbonyl carbon, point 'B' is the nitrogen of the -NH group, point 'C' is the N^+ of the arginine residue and point 'D' is the zinc atom. Figure 2 shows these points superimposed on the first molecule in the data set described below. The distance from point 'A' to point 'C' is determined for most molecules in this set by a bond angle. Because bond angles are held constant during the searches, the AB distance is invariant and of no particular relevance in the sampling studies. Due to the nature of the model and the limited diversity of the molecules, the searches cannot converge to a single point or to a small group of points. Instead, by design, a relatively large volume of distance space is accessible to all molecules.

Figure 3 shows 28 structurally diverse ACE (angiotensin converting enzyme) inhibitors, which were constructed using the Biopolymer Build and Sketch modules in SYBYL 6.0 [9]. The molecules were subjected to full energy minimization using the conjugate-gradient method and the standard Tripos force field [10] to an energy-change convergence criterion of 0.001 kcal/mol. These SYBYL-minimized structures were then used as the starting coordinates for bond length and valence angle minimization in MOPAC 5.0 [11], employing the AM1 model Hamiltonian [12–14] to obtain the final geometries. The initial values of all torsional variables of our molecules were set to 0° (Absolute Orientation). Torsional rotations in all flexible rings were inhibited to maintain correspondence with Mayer's molecules. Rotations around amide bonds were enabled, but restricted to a range of ±10° about cis and trans orientations.

A total of 64 simulations were performed. Four different sampling strategies were applied using each of seven torsional angle increment values (radial distances) ranging from 3° to 10°. For radial sampling, the distances (in Å) equivalent to a rotation of 1° were computed as follows. For every variable torsion of every molecule, the torsion increments generated by a 0.100 Å scan were computed. These values were then summed and averaged to find a scan value that would produce a 1° average scan. For this set of molecules, the scan value was 0.021228673 Å. All degree equivalents for the radial scans were prepared from multiples of this value.

Initial ranges of trial torsion angle values were determined for each torsion variable in each molecule by eliminating angle values that would produce violations of the van der Waals distance constraints for nonbonded atom pairs separated by a single torsional rotation. These ranges were further restricted by removing torsion angle values from each range that would produce partial conformations with locally high steric or torsional energy values. To compute the restricted angle ranges, we used a simplified version of the Tripos force field [10]. Only

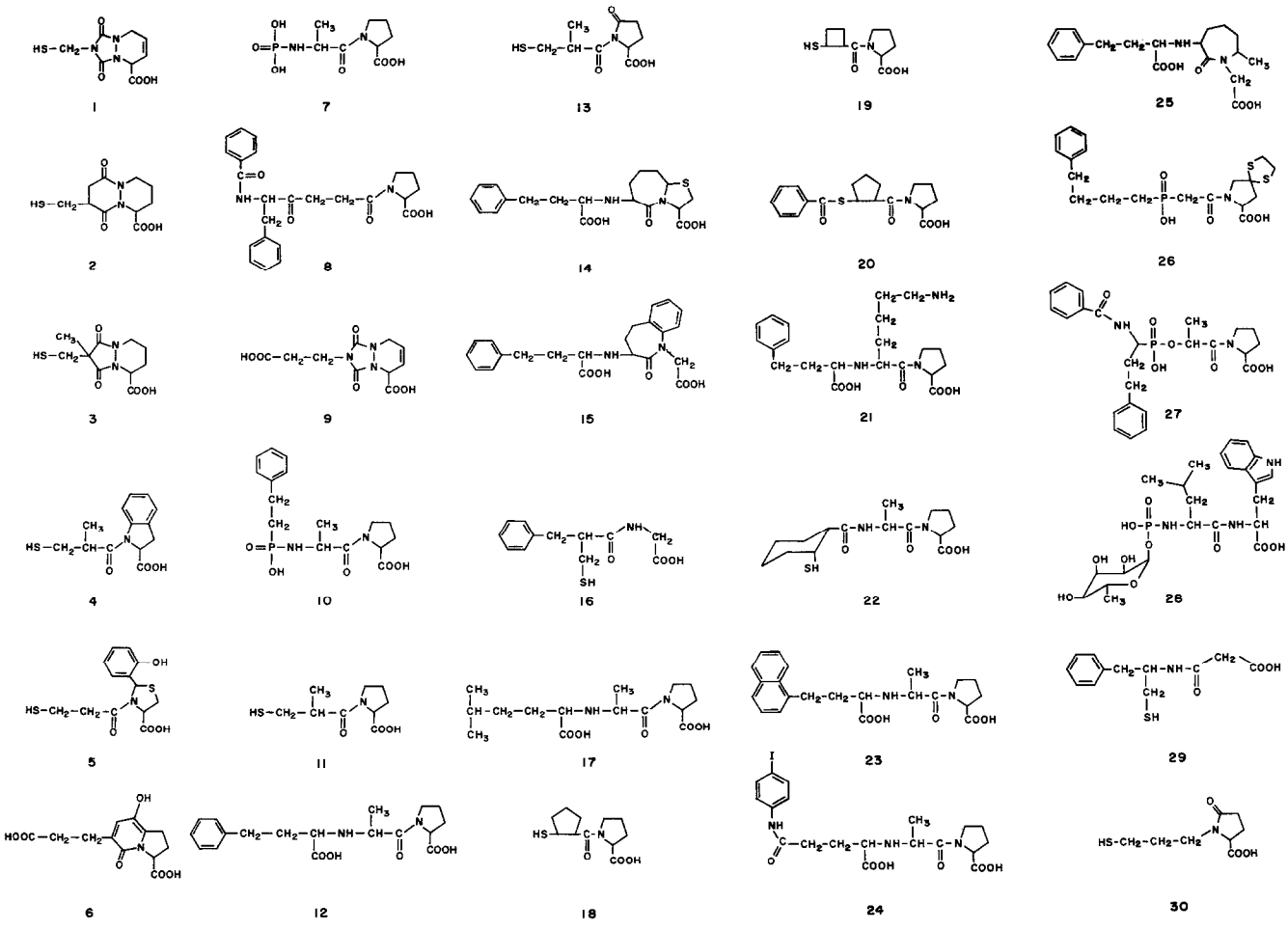

Fig. 3. Molecular structures of 28 ACE inhibitors (**1**–**28**) and two inactive molecules (**29** and **30**) [1].

those atoms directly bonded to the source and reference atoms (S and R as defined above) were considered. For each rotatable bond in each molecule, we calculated steric and torsional energy values at 2° increments (0, 2, 4, ..., 356, 358) for each pair of atoms. One atom is bonded to S and the other to R. These values were summed and averaged to provide a mean torsional energy for each rotation. Values above a specified limit were discarded, typically producing one to four energetically acceptable regions per torsional rotation. A cutoff of 1 kcal/mol above the mean was used for our simulations.

The simulations were performed using classification parameters (hypercube edge lengths) of 0.25 and 0.125 Å to determine the geometric similarity of generated con-

TABLE 1
SAMPLES CLASSIFIED AT HYPERCUBE EDGE LENGTHS OF 0.25 AND 0.125 Å

Degree equivalent	Uniform angle		Uniform radial		Adaptive angle		Adaptive radial	
	0.25 Å	0.125 Å	0.25 Å	0.125 Å	0.25 Å	0.125 Å	0.25 Å	0.125 Å
10	11	0	64	0	149	14	199	42
9	32	0	84	4	127	20	207	59
8	50	0	149	5	206	103	284	126
7	43	0	161	26	182	80	303	199
6	136	7	186	77	255	160	348	257
5	190	39	231	74	251	169	357	278
4	229	120	285	192	309	415	379	461
3	247	201	309	289	348	452	377	592
UNION	265	213	329	349	371	537	467	657
Yield (%)	55.9	30.6	69.4	50.1	78.3	77.2	98.5	94.4

TABLE 2
RESTRICTED SAMPLES CLASSIFIED AT HYPERCUBE EDGE LENGTHS OF 0.25 AND 0.125 Å

Degree equivalent	Adaptive angle		UNION (adaptive angle)		Adaptive radial		UNION (adaptive radial)	
	0.25 Å	0.125 Å	0.25 Å	0.125 Å	0.25 Å	0.125 Å	0.25 Å	0.125 Å
3	348	452			377	592		
4	309	415	348	532	379	461	408	650
5	251	169	368	537	357	278	434	652
7	182	80	371	537	303	199	467	656
Yield (%)			78.3	77.2			98.5	94.4

formers. Using this approach, we were able to assess the relationship between the classification parameter, the torsion angle increment and the quality of the conformational sampling. Standard values of the van der Waals scale factors were used for all searches.

Results

The results shown in Table 1 were obtained from simulations using uniform angle, uniform radial, adaptive angle and adaptive radial sampling. The data values are the number of hypercubes (sample points) corresponding to common orientations of the four functional groups as presented by all 28 molecules. Entries in the row labeled UNION are counts of the logical union of all results for each of the four sampling strategies. Classification parameters of 0.25 and 0.125 Å were used to partition the distance space volume. For these two values, the grand union (the union of the unions) for all simulations contained 474 and 696 distinct sample points, respectively. The yields were calculated by dividing the size of the union obtained for each sampling strategy by the corresponding grand union value.

Table 2 collects the results from simulations where the torsion angle increment was restricted to the values of small relatively prime integers. The union of unions for those simulations contained 474 and 696 distinct sample points for classification parameters of 0.25 and 0.125 Å, respectively. The columns labeled UNION represent the sizes of cumulative unions for each sampling strategy.

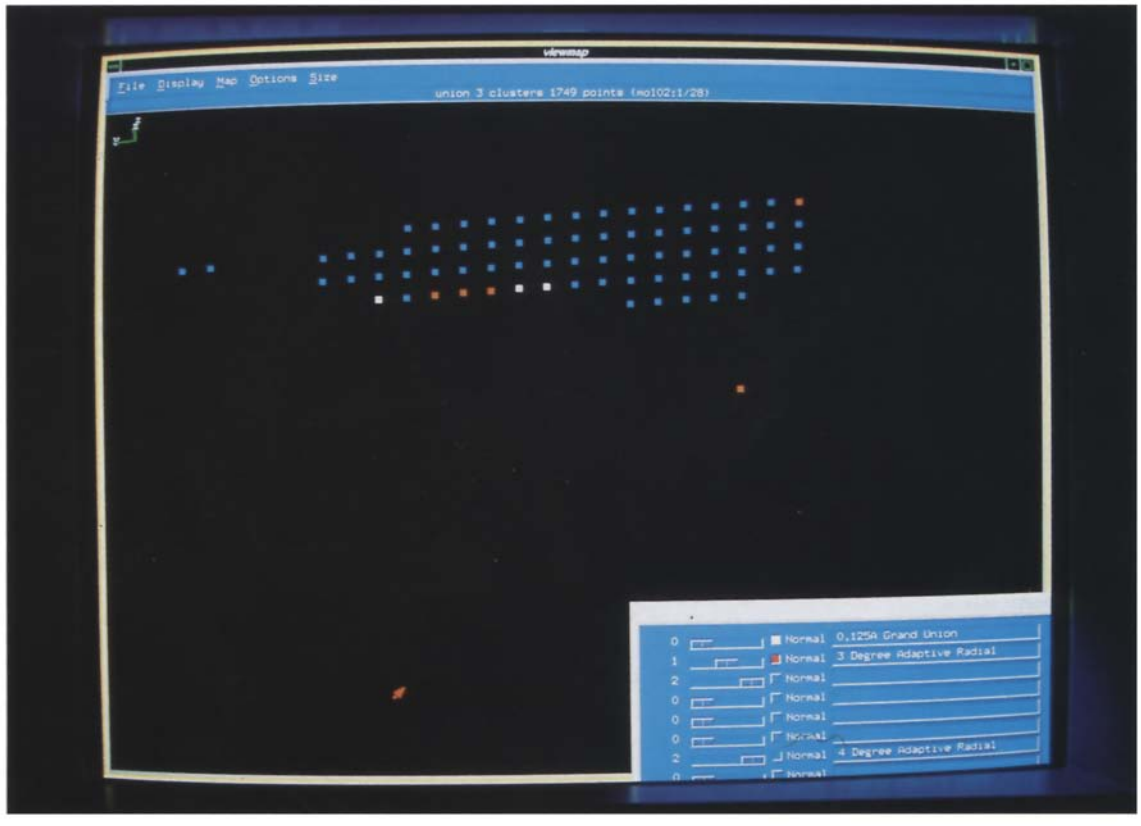

Fig. 4. Projection of the sample points classified at 0.125 Å in the BCD plane.

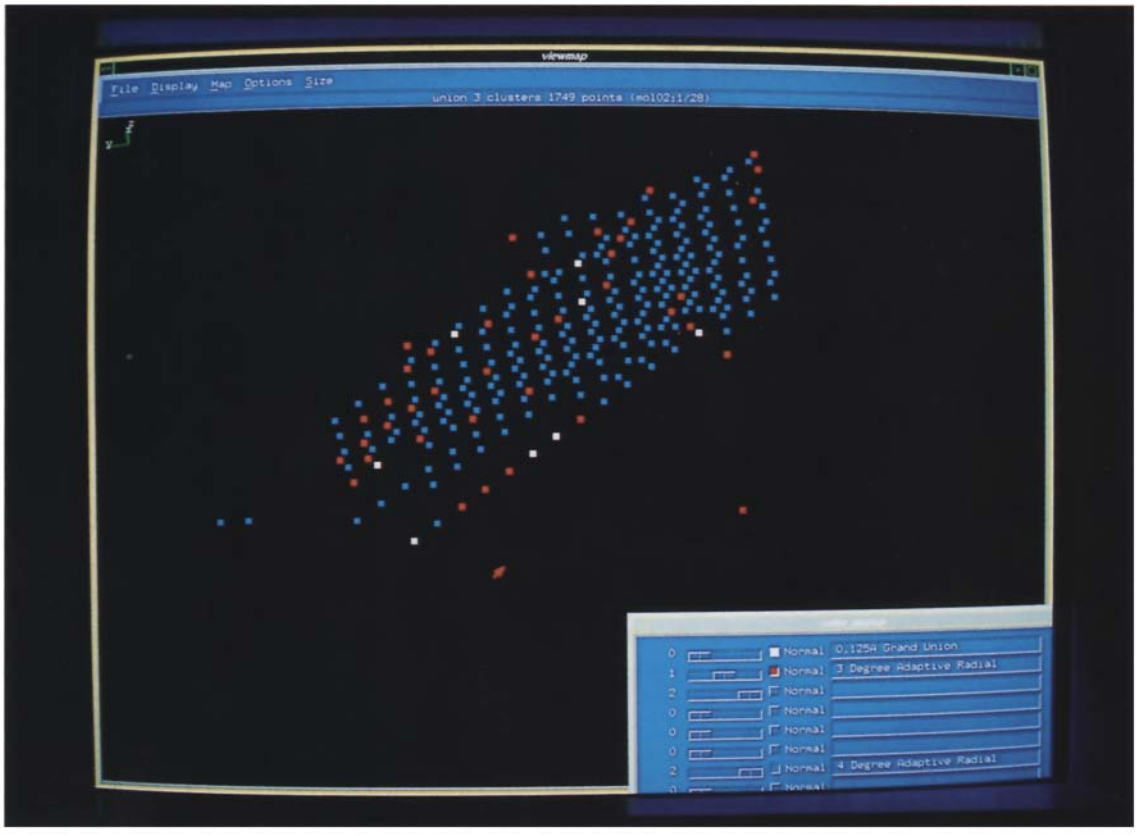

Fig. 5. Perspective view of selected sample points in the BCD subspace.

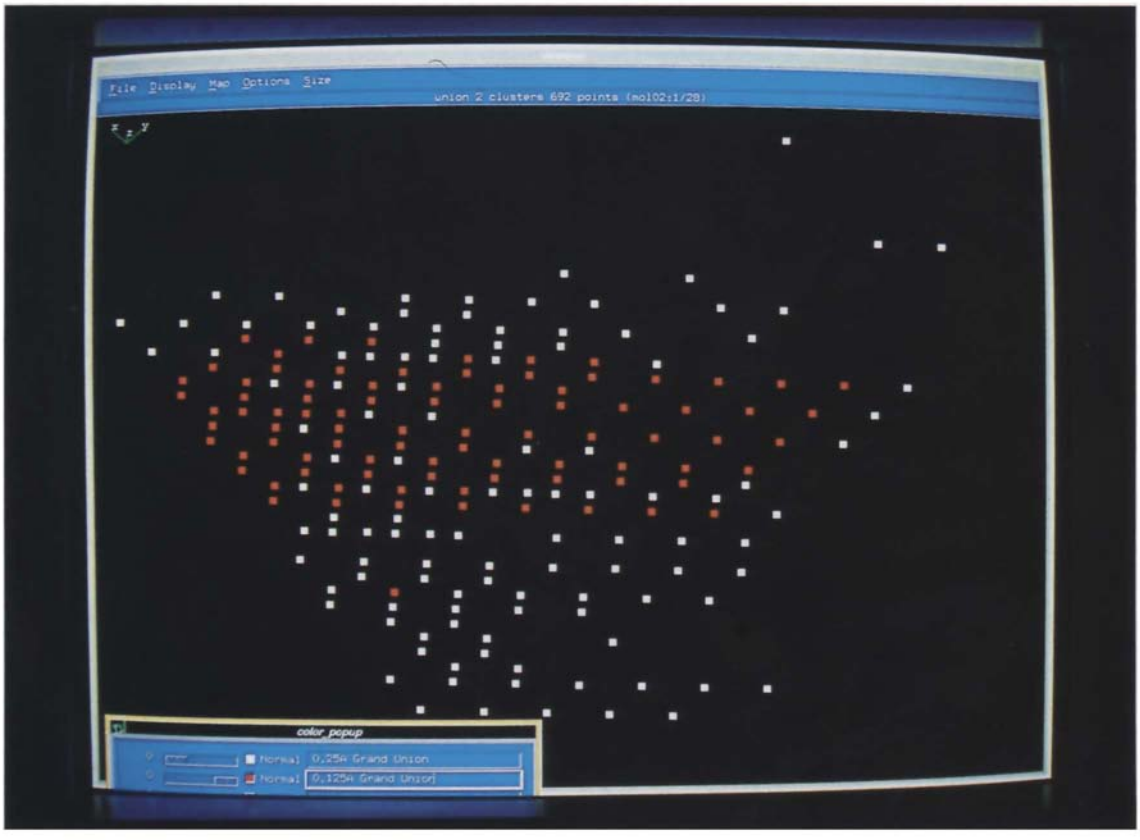

Fig. 6. Perspective view of the union of all sample points in the BCD subspace.

Values in the row labeled 'yield' were obtained by dividing the union by the appropriate grand union value.

The extent of conformation space accessible to all molecules is shown in Table 3. The distances are the minimum and maximum distances between the four functional groups, identified in Fig. 2, contained in the grand union of the sample points for a set of simulations employing the two different classification parameters. The invariant distance AC is not included. A cluster analysis of these data shows that almost all of the points are contained in a single cluster (460 of 474 for the 0.25 Å simulations and 693 of 696 for the 0.125 Å set). The remaining unconnected points were found to be valid results, given the energy cutoff value of 1 kcal above the mean. If this value were reduced slightly, we believe that all points in each set of simulations would be contained in a single cluster.

Figures 4 and 5 show projections of the sample points from the 0.125 Å simulations into a three-dimensional space. Here the axes are the distances between the three site points B, C and D. Figure 4 is an orthogonal view of the BCD plane. The blue squares (cubes) are the results of the 3° adaptive radial sampling experiments. The red squares are the sample points found by the 4° adaptive radial sampling, but missed by the 3° adaptive sample. The white squares are the samples identified by adaptive angle sampling and a classification parameter of 0.125 Å. Figure 5 is a graphic presentation of the same data, viewed from a perspective that highlights the distribution of sample points in the three-dimensional projection. The volume of the space containing the projection is approximately 9 $Å^3$ and contains 123 sample points. The corresponding volume for the 0.25 Å simulations is 28 $Å^3$ and contains 198 sample points. The differences in volume and the number of sample points are a consequence of the more stringent geometric similarity requirement in the 0.125 Å simulations. Figure 6 shows the projection of the union of all sample points from all simulations. Sample points found with a classification parameter of 0.125 Å are shown as red cubes. The white cubes are sample points representing common geometries, which are only similar using the less stringent classification parameter.

TABLE 3
FINAL HYPERSPACE PARTITION USING CLASSIFICATIONS OF 0.25 AND 0.125 Å

Distance	Minimum		Maximum	
	0.25 Å	0.125 Å	0.25 Å	0.125 Å
AB	3.00	3.125	3.50	3.500
BC	3.75	3.750	7.75	6.625
AD	4.25	4.500	5.50	5.500
CD	8.75	9.250	10.50	10.375
BD	3.75	4.500	7.75	7.250

Discussion

In 1989, we demonstrated the fact that multiple searches are an effective way to achieve increased reliability [3]. Using Constrained Search, we performed a series of search experiments with the ACE molecules selected by Mayer et al. [1]. As the adjustable parameter values defining a search were systematically varied, two plausible alternative active-site hypotheses emerged. Subsequent studies were performed by DePriest et al. [15] and Waller et al. [2], who augmented the initial set of 28 molecules with structures from additional classes of ACE inhibitors to resolve the uncertainty represented by consistent, but alternative, hypotheses. In analyzing the results of these new simulations, it is again apparent that no single search experiment is sufficient to fully explore the conformational space common to the set of molecules. In fact, no pure sampling strategy, even if used in multiple searches, identifies all possible sample points. Adaptive radial sampling and a series of searches provided the best (most complete) results. A yield between 94 and 98 percent is probably well within acceptable limits for even the most conservative investigations.

Multiple searches are necessary and quite feasible. When compared to an equivalent Systematic Search, our initial version of Constrained Search reduced the time cost of a single search by three orders of magnitude. Additional algorithmic improvements have been obtained, further reducing the time required by a substantial amount. These improvements involve partitioning conformational space into localized segments, extended look-aheads to eliminate unproductive van der Waals constraint checking and the use of multiprocessors and multiprogramming techniques. Changes in basic data types and structures from individual torsion angle values to ranges of torsional variables produced an unanticipated speed-up of another factor of 20. The ability to search portions of the molecule (such as ring structures) independently and then combine these partial conformations with the residual parts of the whole molecule produced an additional three orders of magnitude reduction in the time required to search structures containing cyclic components. Combined with increases in basic processor speeds, these algorithmic improvements have brought many single search experiments into the interactive realm.

We note that there is a fundamental limitation to any sampling approach. Use of a very small torsion angle increment (a very large number of systematically generated samples) will not produce an absolutely complete sample set. This is due to the underlying mathematical problem of mapping a continuous function onto a discrete set of points. No matter how small the interval, the possibility of nonsampled regions will still exist. The situation is further complicated by the fact that the time cost of sampling grows quadratically as the size (number of atoms) of the molecule increases. Worse yet, the time

cost increases exponentially as a function of the number of torsional variables (internal degrees of rotational freedom). Even though computer speeds have increased dramatically in recent years, we can still only approximate the continuous conformation space.

There may be some applications where it is possible to sample the conformation space at 1° increments. This will be the exception rather than the rule. A pragmatic, cost-effective alternative may be obtained by restricting the torsion angle increments in a series of searches. We observe, by comparing the data in Tables 1 and 2, that a set of torsion angle increments (or increments determined by small radial distances) corresponding to small relatively prime integer numbers produces exactly the same results as those obtained with the full range of typical increment values (10, 9, 8, ...). In addition, it appears that increments of 5° and 7° produce marginal returns when a small (0.125 Å) value is used for the classification parameter. This is shown in Table 2, where searches at 5° and 7° accounted for only two and five distinct points in the adaptive radial sampling simulations, and gave no additional information in the adaptive angle sampling simulations.

In Table 1 it can be seen that uniform angle sampling using a 0.125 Å classification parameter found no sample points common to all 28 molecules, until the angle increment was reduced to 6°. Obviously there is geometric similarity, but it is not discernible with angle increments larger than 6°. In contrast, the results in Table 1 for a classification parameter of 0.25 Å indicate commonality with an increment as large as 10°. We believe that this is indicative of a causal relationship between the torsion angle increment and the hypercube edge length (i.e., small edge lengths for partitioning require the use of small torsion angle increments or radial distances). The failure to recognize this relationship is more than likely the cause of 'problem molecules' that cause a search experiment to terminate without finding any common sample points. The failure is not necessarily a sign of an invalid pharmacophore or active-site hypothesis. Rather, the difficulty may be in the selection of incompatible search parameters. We currently believe that the radial distance used in sampling should not be larger than one half the hypercube edge length. Further investigations are planned in order to explore this aspect of designing an effective set of search experiments.

Conclusions

Adaptive radial sampling is apparently a better sampling strategy than the fixed grid sampling strategies that have been used previously. Even so, we recommend that a series of adaptive radial sampling experiments be performed in each application of the Active Analog Approach [6], restricting the radial sampling increments to equivalents of torsion angle increments of 3°, 4° and 5°. An even more complete sample of conformational hyperspace may be obtained by combining the results of a series of search experiments using both adaptive radial and adaptive angle sampling. In addition to the simulation results reported here, we have also performed experiments comparing the results of searches of small cyclic compounds using adaptive sampling to those obtained with other sampling strategies. We found that grid searches, particularly those using a fixed integer angle sampling value, fail to find many of the known, closed conformations of such molecules. These additional results will be presented in a subsequent publication.

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References

1 Mayer, D., Naylor, C.B., Motoc, I. and Marshall, G.R., J. Comput.-Aided Mol. Design, 1 (1987) 3.
2 Waller, C.L., Shands, E.B.F., Dammkoehler, R.A. and Marshall, G.R., J. Comput.-Aided Mol. Design, manuscript submitted for publication.
3 Dammkoehler, R.A., Karasek, S.F., Shands, E.F.B. and Marshall, G.R., J. Comput.-Aided Mol. Design, 3 (1989) 3.
4 Iijima, H., Dunbar, J.B. and Marshall, G.R., Protein Struct. Funct. Genet., 2 (1987) 330.
5 Motoc, I., Dammkoehler, R.A. and Marshall, G.R., In Trinajstic, N. (Ed.) Mathematics and Computational Concepts in Chemistry, Ellis Horwood, Chichester, 1986, pp. 222–251.
6 Marshall, G.R., Barry, C.D., Bosshard, H.E., Dammkoehler, R.A. and Dunn, D.A., In Olson, E.C. and Christoffersen, R.E. (Eds.) Computer-Assisted Drug Design, ACS Symposium Series Vol. 112, American Chemical Society, Washington, DC, 1979, pp. 205–226.
7 Bruccoleri, R.E. and Karplus, M., Macromolecules, 18 (1985) 2767.
8 Gō, N. and Scheraga, H.A., Macromolecules, 3 (1970) 178.
9 SYBYL, v. 6.0, Tripos Associates, St. Louis, MO.
10 Clark, M., Cramer III, R. and Van Opdenbosch, N., J. Comput. Chem., 10 (1989) 982.
11 MOPAC, v. 5.0, QCPE Program No. 455, Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN, 1991.
12 Dewar, M.J.S., Zoebisch, E.G., Healy, E.F. and Stewart, J.J.P., J. Am. Chem. Soc., 107 (1985) 3902.
13 Dewar, M.J.S. and Jie, C., THEOCHEM, 187 (1989) 1.
14 Dewar, M.J.S. and Yuan, Y.C., Inorg. Chem., 29 (1990) 3881.
15 DePriest, S.A., Mayer, D., Naylor, C.B. and Marshall, G.R., J. Am. Chem. Soc., 115 (1993) 5372.