Scaffold Topologies. 1. Exhaustive Enumeration up to Eight Rings

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Received September 13, 2007

Mapping the chemical space of small organic molecules is approached from a theoretical graph theory viewpoint, in an effort to begin the systematic exploration of molecular topologies. We present an algorithm for exhaustive generation of scaffold topologies with up to eight rings and an efficient comparison method for graphs within this class. This method uses the return index, a topological invariant derived from the adjacency matrix of the graph. Furthermore, we describe an algorithm that verifies the adequacy of the comparison method. Applications of this method for chemical space exploration in the context of drug discovery are discussed. The key result is a unique characterization of scaffold topologies, which may lead to more efficient ways to query large chemical databases.

1. INTRODUCTION

The question of how vast is the chemical space of small organic molecules (CSSM) has been addressed in several ways—all of them related to *in silico* technologies, such as virtual chemical library enumeration starting from known lists of reagents. For example, the effort of enumerating all derivatives of *n*-hexane, from mono- to 14-substituted hexanes, starting from a list of 150 substituents, exceeds 10^{29} unique structures.[1] Although most of these hexane derivatives might be, to date, synthetically inaccessible, a small number of building blocks can lead to an unlimited number of possibilities, as witnessed in living systems: 22 proteinogenic amino acids and five nucleotides combine to form large arrays of proteins and nucleic acids, respectively. Representatives of all of the “tangible” chemicals[2] (on the order of 100 million physical compounds) can be collected and catalogued, and starting from such a database, one could, in theory, expand into the space of virtual chemistry. However, there is currently no approach that would enable the systematic exploration of this chemical space. Indeed, most methods explore only the limited space covered by (a) known chemical reactions and (b) available/known chemical reagents. The question of how large this chemical space really is has relevance if one considers that adequate sampling[2] is required, should one desire to query biological end points using a diverse set of small molecules. To date, the CSSM has been systematically mapped for organic molecules with 11 or less main atoms and a molecular weight of less than 160 Da.[3] Eliminating constrained structures, the total number of chemicals produced was approximately 44 million. A chemical database of synthetically feasible structures is available at http://www.dcb.unibe.ch/groups/reymond/. In another study,[4] orderly generation was used to produce all possible single-bonded carbon graphs ranging from a maximum of 20 atoms and two rings to 13 atoms and eight rings. A total of about 1.45 billion graphs were generated,[5] but this effort was never completed. Thus, the process of exhaustively mapping the CSSM is far from trivial, even when the effort is restricted to graph-reduced scaffolds.

In this paper, we map the CSSM for all molecules containing eight or fewer independent rings and any number of atoms, by systematically exploring the topologies that can be present in the CSSM at the graph level, that is, carbon-based, single-bond scaffolds only. The exploration of scaffolds is critical, since with few exceptions medicinal chemistry-based drugs contain scaffolds. We reduce the discussion of scaffolds to their corresponding topologies, a description of the connected ring structure of a class of scaffolds. In this paper, we show how the complete set of scaffold topologies (up to a given size) may be algorithmically generated and uniquely characterized. The space of possible scaffolds may be partitioned by topology class so that the union of topology classes is precisely the space of possible scaffolds. We present results for the population of topologies in systems up to and including eight rings. In a companion paper,[6] we examine a number of chemical databases, some large and general, some smaller and more biologically oriented, for the properties of their topologies. We compare the results with the complete coverage developed here for molecules with up to and including eight rings.

2. BASIC CONCEPTS

A *graph*, G, sometimes called a *pseudograph*,[7] is a collection of *nodes* and *edges* such that each edge connects exactly two not-necessarily distinct nodes. Denote the set of nodes by $V(G) = \{v_1,v_2,. . .,v_n\}$. A *walk* is a sequence of contiguous edges, or equivalently, a sequence of connected nodes, from v_i to v_j, and a *path* is a walk in which each node is traversed at most once. A *cycle* is a path starting and ending at v_i. In a *connected graph*, any two distinct nodes are connected by at least one path. All graphs we consider in this analysis are connected graphs. A graph may be described by any of its corresponding adjacency matrices.

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10.1021/ci7003412 CCC: $40.75

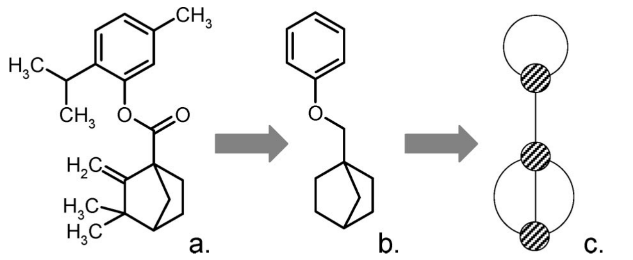


Figure 1. (a) (5-Methyl-2-propan-2-yl-phenyl)-3,3-dimethyl-2-methylidene-bicyclo[2.2.1]heptane-1-carboxylate. (b) The scaffold corresponding to this molecule. (c) The topology corresponding to this scaffold.

An *adjacency matrix* of a graph, **A**, is a symmetric matrix, where each entry (a_{ij}) counts the edges connecting v_i and v_j. A graph with n nodes may be described by any of up to $n!$ adjacency matrices of size $n \times n$ which are equivalent up to the permutation of indices. These matrices are considered *isomorphic*. The *degree* of node v_i is its row (or equivalently, column) sum, which describes the number of edge segments incident to node v_i: $\deg(v_i) = \sum_{j=1}^{n} a_{ij}$. Each edge has two terminal segments, and an edge with both terminal segments incident to a node v_i is called a *loop* and increments $\deg(v_i)$ by two. A node of degree k is called a k-node, and l edges connecting the same pair of nodes are called an l-edge. A graph with multiple edges between the same nodes but without loops is called a *multigraph*, while a graph without multiple edges or loops is called a *simple graph*.[7] The problem of deciding if there exists a relabeling of indices that makes the adjacency matrices of two given graphs coincide is called the graph isomorphism problem.[8] In general, the recognition of the isomorphism of simple graphs with bounded valences can be carried out in polynomial time[9] and of all graphs in moderately exponential time, $O(e^{\sqrt{(n \log n)}})$, where n is the number of nodes in the graph.

In this discussion, a *scaffold topology*, or *topology*, is a connected graph with the minimal number of nodes and corresponding edges required to fully describe its ring structure. We limit this analysis to topologies with a maximum nodal degree of four, corresponding to the valence of neutral carbon. Except for the graph consisting of exactly one ring (one node with a loop), topologies contain nodes exclusively of degrees three and four. The one-ring graph is referred to as an *isolated loop*.

A *scaffold*, in this context, is a chemical graph composed solely of rings and optional linking linear structures. All branches of a scaffold terminate in a ring. This description is functionally equivalent to the one found in Koch et al.[10] and Bemis and Murcko[11] (where it is called a molecular framework). We prefer the terms *scaffold* and *scaffold topology* to emphasize its theoretical, chemistry-free nature. At this level, the objects contain only topological information, as defined above. A molecule with its corresponding scaffold and topology is shown in Figure 1. We limit this discussion to scaffolds containing only single bonds and a maximum atomic valence of four. Any such scaffold may be constructed from exactly one topology by distributing 2-nodes along its edges, expanding each edge in the topology into a chain of one or more edges. To describe the space of carbon-based single-bond scaffolds with, say, 25 atoms, let $n_d = 25 - n$, the number of 2-nodes to distribute in a graph with n nodes and e edges. Then, a sharp upper bound for the number of scaffolds, $n_{\text{scaffolds}}$, that may exist in each (n, e) topology class is

$$n_{\text{scaffolds}} \le \binom{e + n_d - 1}{n_d}$$

with equality if and only if there are no equivalent edges in the topology. Two edges, e_i and e_j, are considered *equivalent* if the graphs resulting from attaching an isolated loop to each of e_i and e_j, respectively (as seen in Figure 3, case 3), differ only by permutation of the indices.

Let n denote the total number of nodes in a graph and N_k denote the number of k-nodes.

Summing over nodal degrees gives $n = \sum_{k \geq 1} N_k$.

For scaffolds, $n = N_2 + N_3 + N_4$, and for topologies with $4 \geq n \geq 3$, $n = N_3 + N_4$.

Let e count the total number of edges in a graph; then, $2e = \sum_{k \geq 1} kN_k$.

For scaffolds, $2e = 2N_2 + 3N_3 + 4N_4$, and for topologies with $4 \geq n \geq 3$, $2e = 3N_3 + 4N_4$.

The number of *independent rings*, referred to in this analysis as the number of rings, is equivalent to Cauchy's *nullity*, $\mu = r = e - n + 1$.

For topologies with $4 \geq n \geq 3$, $r = N_4 + N_3/2 + 1$. Holding N_4 constant, N_3 increments by two as r increments by one.

3. GENERATING TOPOLOGIES

All topologies with r rings and j 4-nodes may be generated by at least one topology with r rings and $j - 1$ 4-nodes by "fusing" together a pair of connected 3-nodes into a single 4-node in an otherwise identical graph.

A 4-node without any loops may connect to

(i) four distinct nodes by 1-edges

(ii) three distinct nodes: two by 1-edges and one by a 2-edge

(iii) two distinct nodes by 2-edges, or one by a 1-edge and one by a 3-edge

(iv) one distinct node by one 4-edge

A 4-node with loops may connect to

(ii-a) two distinct nodes by 1-edges and one loop

(iii-a) one distinct node by a 2-edge and one loop, or two loops

In case i, the 4-node may be constructed three ways. In cases ii, ii-a, iii with 2-edges, and iii-a, the 4-node may be constructed two ways. In case iii with a 3-edge and case iv, the 4-nodes may be constructed one way, see Figure 2.

Denote the family of topologies with r rings, N_3 3-nodes, and N_4 4-nodes by (r, N_3, N_4). For a particular r and N_4, we may generate all topologies in (r, N_3, N_4) from the family (r, $N_3 + 2$, $N_4 - 1$), $1 \leq N_4 \leq r - 1$, where $N_3 = 2(r - N_4 - 1)$.

As a topology is the reduced form of a family of scaffolds, where the corresponding scaffolds may break up any edge in a topology into a chain of contiguous edges, we may consider edge i in a topology to contain any number of "virtual" 2-nodes, $u_{i,k}$, $i = 1, 2, \ldots, e$ and $k = 1, 2, \ldots$; that is, in a graph with n nodes, an edge may be added by connecting $u_{i,k}$ to $u_{j,l}$, which then acquire degree three and become v_{n+1} and v_{n+2}, respectively.

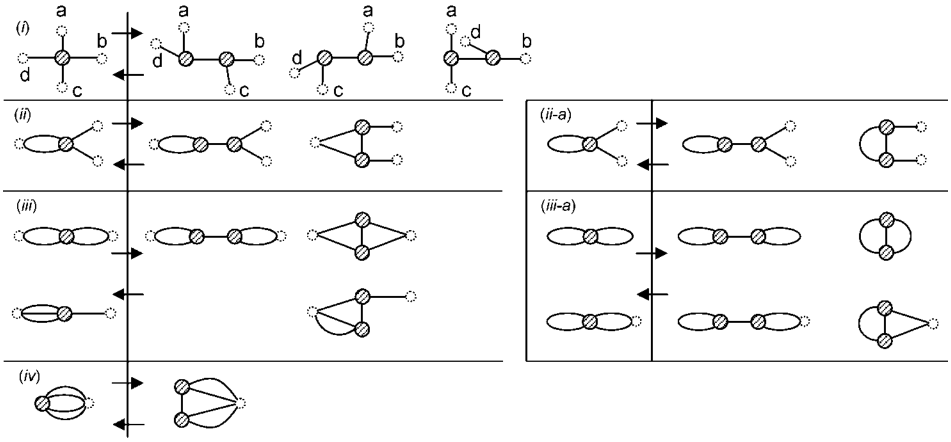


Figure 2. Three operations to increment *r* by 1 and N_3 by 2.

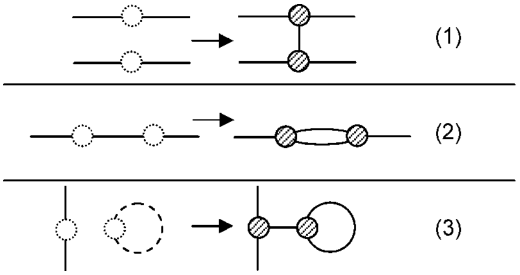


Figure 3. The correspondence between 4-nodes and pairs of connected 3-nodes.

There are three ways to increment the number of 3-nodes in a topology holding N_4 constant: $(r, N_3, N_4) \rightarrow (r + 1, N_3 + 2, N_4)$, where $N_4 = r - N_3/2 - 1$.

(1) connecting $u_{i,k}$ to $u_{j,l}$, $i \neq j$

(2) connecting $u_{i,k}$ to $u_{i,l}$

(3) connecting $u_{i,k}$ to u_{loop}, where u_{loop} denotes the 2-node of an isolated loop (the isolated loop may also be considered "virtual" until it is connected to the topology via an edge). See Figure 3 for details.

With these three operations to increment *r* by one, *e* by three, and N_3 by two, and a single operation to decrement N_3 by two and *e* by one and increment N_4 by one, we may generate all topologies with a given number of rings by starting with any complete family of topologies containing only 3-nodes: $(r, 2(r - 1), 0)$. We choose to start with the two topologies in (2, 2, 0), see Figure 4.

The completeness of the generation scheme follows from the following two observations:

(1) If, in a graph with N_3 3-nodes and N_4 4-nodes and thus $r = N_3/2 + N_4 + 1$ rings, we replace one 4-node by two 3-nodes by following any of the steps in Figure 2 from left to right, there results a graph with $N_4 - 1$ 4-nodes and $N_3 + 2$ 3-nodes, the same number of rings and one less edge.

(2) In a graph containing only 3-nodes, there are only three ways to remove an edge, given by the reverse of each of the steps shown in Figure 3. Hence, if we consider any graph containing N_3 3-nodes and zero 4-nodes, and thus $r = N_3/2 + 1$ rings, and we remove any edge by the reverse of moves of type 3(1) or 3(2) such that the graph remains connected and also remove the resulting 2-nodes, or if we remove a loop, its associated node, and the node connected to it (the reverse move of 3(3)), we end up with a graph with $N_3 - 2$ 3-nodes, and consequently $r - 1$ rings (and three fewer edges). Now, if we assume that we have all possible graphs with N_3 3-nodes and zero 4-nodes, it follows from observation 2 above that we will get all possible graphs with $N_3 + 2$ 3-nodes and zero 4-nodes (and $r + 1$ rings). Beginning with all possible graphs with two 3-nodes (the two graphs shown in Figure 4), it follows by induction that we may generate all possible graphs with arbitrary (but even) numbers N_3 of 3-nodes and zero 4-nodes (and thus $r = N_3/2 + 1$ rings). And, following observation 1, if we assume that we have all possible graphs with N_3 3-nodes and N_4 4-nodes and $r = N_3/2 + N_4 + 1$ rings, then we may get all possible graphs of $N_3 - 2$ 3-nodes and $N_4 + 1$ 4-nodes by following all possible moves shown in Figure 2 from right to left. This process may be repeated until we generate all possible graphs with zero 3-nodes and $r - 1$ 4-nodes.

4. RETURN-INDEX

The algorithm described above generates all possible topologies, but due to symmetries, it generates many topologies more than once. To enumerate the complete collection of distinct topologies, we compare each topology with the members of its (r, N_3, N_4) class. As mentioned previously, a graph with *n* nodes has up to *n!* associated adjacency matrices, considered isomorphic. It is possible to avoid comparing *n!* matrix permutations, as would be required to determine isomorphism from adjacency matrices directly. Several algorithms exist for solving the graph isomorphism problem efficiently for different categories of graphs, among which McKay's package ***nauty***[12] is considered state-of-the-art for both exhaustive generation and solution of the isomorphism problem.[13] The most relevant algorithms in ***nauty*** for our purpose are ***GENG***, which may produce an exhaustive enumeration of simple graphs that may include up to one loop per vertex but not multiedges; ***LABELG***, which produces a canonical labeling of all simple graphs of the type generated by GENG; and ***MULTIG***, which can generate all possible distinct multigraphs corresponding to a given simple graph with no loops and test them for isomorphism (but does not produce a canonical labeling). Since pseudographs with both loops and multiedges are not allowed,[12] one would need to include 2-nodes and then prune the graphs thus generated, removing all 2-nodes and discarding equivalent graphs. Although it could be possible to use this approach with some effort, it would result in huge numbers of redundant structures that would have to be generated, pruned, and compared. There have been other

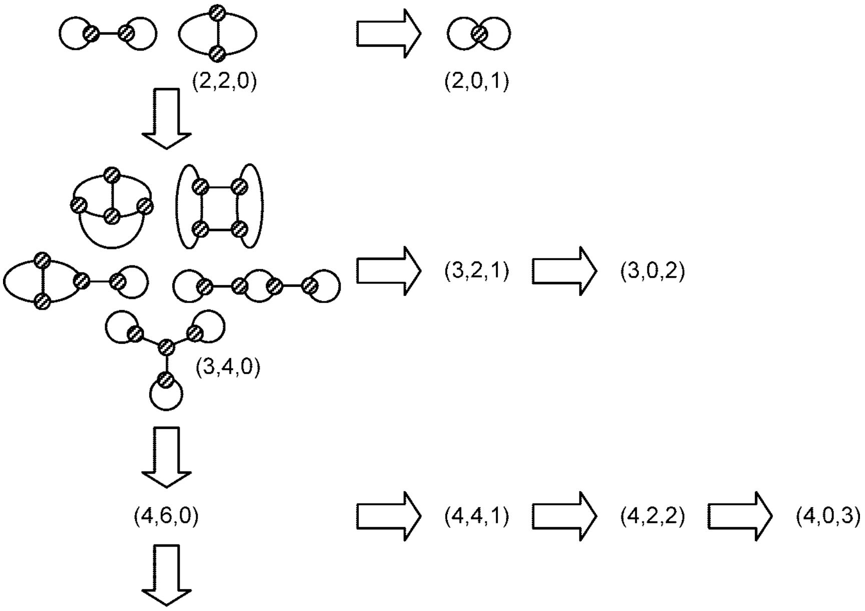
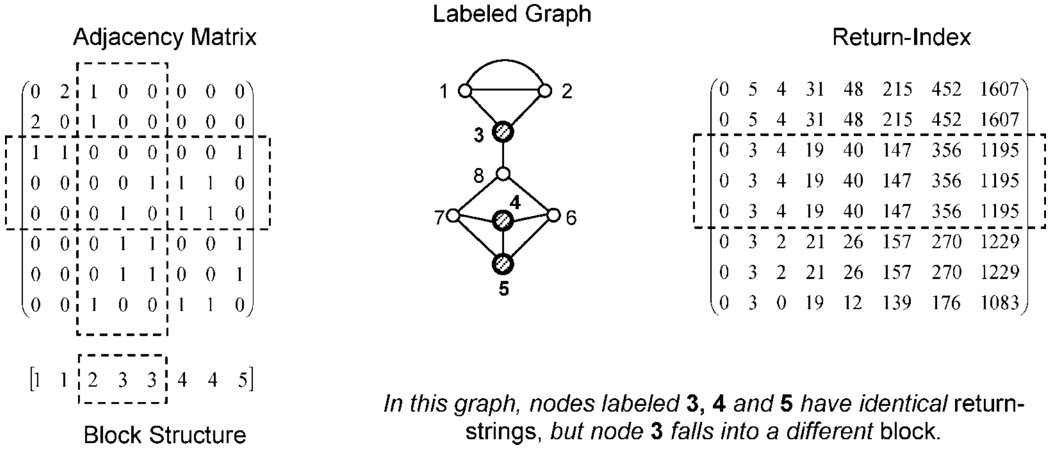


Figure 4. Schematic diagram of the generation scheme showing all graphs in (2, 2, 0), (2, 0, 1), and (3, 4, 0).



Adjacency Matrix

$$\begin{pmatrix} 0 & 2 & 1 & 0 & 0 & 0 & 0 & 0 \\ 2 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 \end{pmatrix}$$

$$[1 \quad 1 \quad 2 \quad 3 \quad 3 \quad 4 \quad 4 \quad 5]$$

Block Structure

Return-Index

$$\begin{pmatrix} 0 & 5 & 4 & 31 & 48 & 215 & 452 & 1607 \\ 0 & 5 & 4 & 31 & 48 & 215 & 452 & 1607 \\ 0 & 3 & 4 & 19 & 40 & 147 & 356 & 1195 \\ 0 & 3 & 4 & 19 & 40 & 147 & 356 & 1195 \\ 0 & 3 & 4 & 19 & 40 & 147 & 356 & 1195 \\ 0 & 3 & 2 & 21 & 26 & 157 & 270 & 1229 \\ 0 & 3 & 2 & 21 & 26 & 157 & 270 & 1229 \\ 0 & 3 & 0 & 19 & 12 & 139 & 176 & 1083 \end{pmatrix}$$

In this graph, nodes labeled **3, 4** *and* **5** *have identical* return-strings, *but node* **3** *falls into a different* block.

Figure 5. Example of topologically inequivalent nodes with the same return string.

attempts to separate pseudographs into equivalence classes via a labeling scheme and then explore the corresponding chemical space. Lipkus[14] classifies the CSSM with a trio of topological descriptors, while Xu and Johnson[15,16] used molecular equivalence numbers, which produce finer-grained classes than our topologies, but the method was potentially subject to classification noise.

These considerations led us to seek a direct approach, one that would work for the scaffold-topology-type graphs considered here. In general, a graph may be associated with a diverse set of topological invariants that are independent of the specific indexing. Such invariants which both possess discriminating power and can be computed in polynomial time may help reduce the isomorphism problem. Different types of invariants have been introduced by various authors (see, e.g., Ivanciuc et al.[17] and the references therein). One such set of invariants consists of the eigenvalues of the adjacency matrix, the *spectrum* of the graph.[18] It is well-known that the spectrum of a graph does not fully discriminate between graphs, in that *isospectral* but nonisomorphic graphs do exist.[19] For our purposes, we were able to arrive at a simple, discriminating method for comparing scaffold topologies with up to eight rings that can be carried out in polynomial, $O(n^3)$ time, as well as a unique characterization for such graphs, by introducing the *ordered return index*.

Let a k-walk denote a walk of length k. It is well-known[7] that the entries of A^k, $(a_{ij}^{(k)})$, contain the number of k-walks from v_i to v_j. In particular, $(a_{ij}^{(k)})$ contains the number of *return walks*, starting and ending at v_i. We construct the *return index*, **R**, an $n \times n$ matrix whose columns, $R^{(k)}$, contain the diagonal entries of A^k, $(a_{jj}^{(k)})$, $j = 1, 2, \ldots, n$. In practice, **R** is constructed by taking the powers of **A**′, the adjacency matrix with all entries on the main diagonal set to zero. No information is lost as all nodes in **A** are of degree three or four, and subtracting loops leaves affected nodes with degree zero, one, or two, respectively, distinguishing them from other nodes in the topology. The degree is zero in exactly one case, depicted in Figure 4, where the single node with two loops is the only member of the family (2, 0, 1). The first column of **R** (return walks of length one) does not contain any distinguishing information and is replaced with the number of 1-nodes each respective node has as first-order neighbors in **A**′, in a linear-time algorithm. The full calculation of **R** is a cubic-time algorithm. Each column of **A** (or **A**′) has at most four entries, and the calculation of

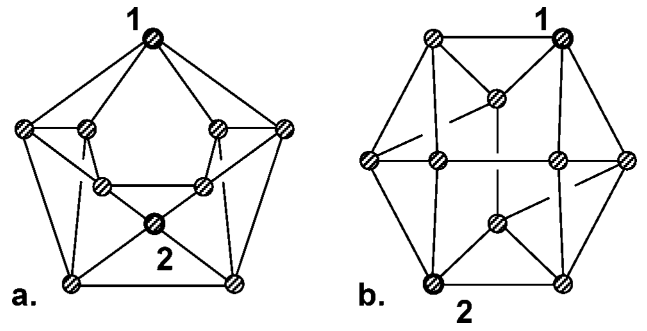


Figure 6. In graph a, nodes labeled **1** and **2** have identical *return strings* but fall into different blocks. In graph b, nodes labeled **1** and **2** have identical *return strings* and fall into the same block. Graphs a and b have identical *return indices* but different *block structures*.

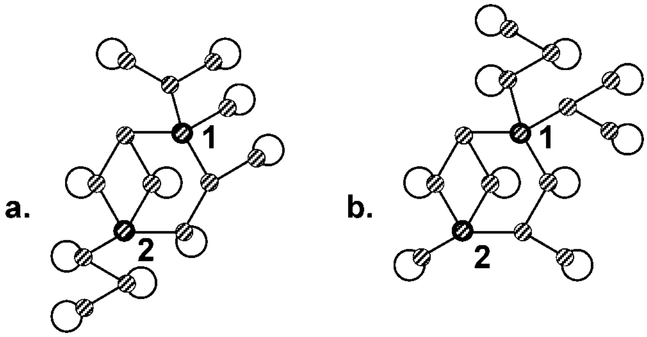


Figure 7. In both graphs a and b, nodes labeled **1**and **2** have identical *return-strings*, but fall into different blocks. Graphs a and b have identical *return indices* and *block structures* but are not isomorphic.

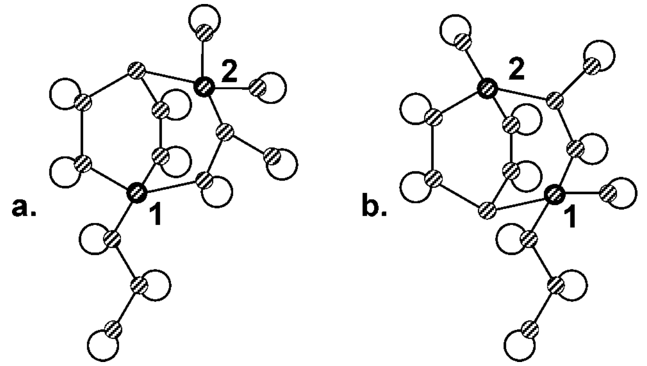


Figure 8. In both graphs a and b, nodes labeled **1** and **2** have identical *return strings* but fall into different blocks. Graphs a and b have identical *return indices*, but they have different respective *block structures*. With the *return index* modified to contain the number of 1-node neighbors instead of return walks of length 1, graphs a and b are fully distinguished without comparing block structures.

each power is at most $4n^2$ operations. Since we need to calculate $n - 1$ powers, the total operations count is on the order of n^3.

The rows of **R**, each of which contains information with respect to a particular node of **A′**, may be sorted in descending numerical order. The row **R′** corresponding to node v_i is its *return string*. The ordered matrix, **R′**, may be used to compare graphs. It is clear that two graphs with different return indices are not isomorphic. It is not true in general that two graphs with the same ordered return index are necessarily isomorphic. We demonstrated by exhaustive pairwise comparison that, for topology graphs of up to and including eight rings, the ordered return index fully distinguishes nonisomorphic graphs (data not shown). These topologies can be queried interactively at the UNM Biocomputing Web site.[20]

5. VERIFICATION OF THE ORDERED RETURN INDEX

To verify that **R′** fully discriminates topologies up to a certain size, we ran the generation algorithm, comparing topologies by **R′**. Where **R′** matched another previously generated topology in the corresponding (r, N_3, N_4) class, adjacency matrices were compared using all possibly equivalent graph labelings until we found a match. The determination of possibly equivalent labelings is described below. In all cases where the return indices of two graphs matched, some permutation (labeling) of the adjacency matrices matched as well. In order to reduce the number of permutations and comparisons, the graphs are first assigned a semicanonical numbering with respect to the return string corresponding to each node. The graph is then labeled in terms of "blocks" ,where each block contains nodes with the same return string. We implement the following recursive algorithm:

(1) For each node, form a neighbor list specifying to which blocks its first-order neighbors belong.

(2) Reorder nodes within existing blocks according to the neighbor lists.

(3) Relabel the graph with a new set of blocks separating previous blocks by neighbor lists.

(4) If any new blocks were created in 3, and there are less than n blocks, return to 1. This algorithm is guaranteed to terminate in less than n steps, as the number of blocks cannot exceed the number of nodes. The *block structure* is the final list of blocks corresponding to the reordered list of nodes; by construction, the block structure is arranged in ascending numerical order. The members of each block in the final block structure are called *topologically equivalent* nodes. Two isomorphic graphs must have the same block structure. In comparing adjacency matrices, graphs are first relabeled in terms of their block structure. Only indices falling within the same blocks need be permuted in order to find a match between matrices. An example of topologically inequivalent nodes with the same return string is shown in Figure 5.

A useful byproduct of having established that the ordered return index has discriminatory power when applied to scaffold topologies with up to eight rings is the unique characterization for such graphs. Indeed, if we tag each such graph with its ordered return index, we have shown that identical ordered return indices imply isomorphism. The actual proof of this fact still requires permutation and comparison, since the method does not result in a canonical labeling of the nodes of a pseudograph, but rather a division of the nodes of a graph into topologically descriptive subclasses. Thus, the nonisomorphism of two graphs with distinct ordered return indices is automatic. In order to establish adequacy of the return index for determining isomorphism in case of identical ordered return indices, we need to compare all possible reindexings of topologically equivalent nodes. This process, although much reduced relative to a full comparison of all permutations, can still be daunting. However, once carried out for all possible topolo-

Table 1. Total Number of Distinct Topologies up to and Including Eight Rings

		N_3								
		0	**2**	**4**	**6**	**8**	**10**	**12**	**14**	total
	1	1								1
	2	1	2							3
	3	2	5	5						12
r	**4**	4	22	30	17					73
	5	10	88	228	193	71				590
	6	28	430	1655	2457	1496	388			6454
	7	97	2242	12905	28301	28649	13343	2592		88129
	8	359	13239	105188	326761	483124	365994	136666	21096	1452427

gies of up to eight rings, we found that the ordered return index is indeed adequate to distinguish all such topologies. Having established this, we have thus reduced the problem of detecting graph isomorphism of scaffold topologies, that is, pseudographs of valence three or four with eight or fewer rings to the simple, polynomial time computation of the ordered return index and the linear time comparison of the indices of two graphs.

6. COUNTEREXAMPLES WITH MORE THAN EIGHT RINGS

The return index, even without the additional discrimination provided by the neighbor ranking, has at least the same discriminating power as the spectrum. This is a consequence of the fact that a matrix satisfies its own characteristic polynomial (Cayley–Hamilton theorem[21]). Thus, if the characteristic polynomial is given by

$$P(\lambda) = \lambda^n + p_{n-1}\lambda^{n-1} + \ldots + p_1\lambda + p_0$$

then, since $P(A) = 0$, it follows that

$$a_{ii}^{(n)} + p_{n-1}a_{ii}^{(n-1)} + \ldots + p_1 a_{ii} + p_0 = 0; i = 1, \ldots, n$$

so that the coefficients of the characteristic polynomial can be determined completely from the entries of the return-index matrix **R**, since there are n equations in the n quantities p_i, $i = 1, \ldots, n$. Thus, graphs with the same return index have the same characteristic polynomials and are therefore isospectral.

The following three pairs of topologies are not differentiated by the return index, if it is calculated without replacing the first column of **R** with 1-node neighbor information; with that modification, the third pair is distinguished. The topologies in the first pair, with 11 rings, found among various examples on isospectral graphs in Cvetkovič et al.,[19] have identical return indices but different block structures (Figure 6). The topologies in the second pair, with 12 rings, have identical return indices and block structures (Figure 7). These graphs are not isomorphic, as can be shown by permutation of indices within blocks of topologically equivalent nodes, or by the observation that there is no node in graph a with the same branching structure as that of node 1 in graph b. The topologies in the third pair, with 13 rings, have identical return indices but different block structures (Figure 8). All three pairs of graphs contain a pair of nodes with equivalent return strings, but which fall into different blocks in at least one of the two graphs in the pair. We have not determined whether there are any counterexamples with 9 or 10 rings.

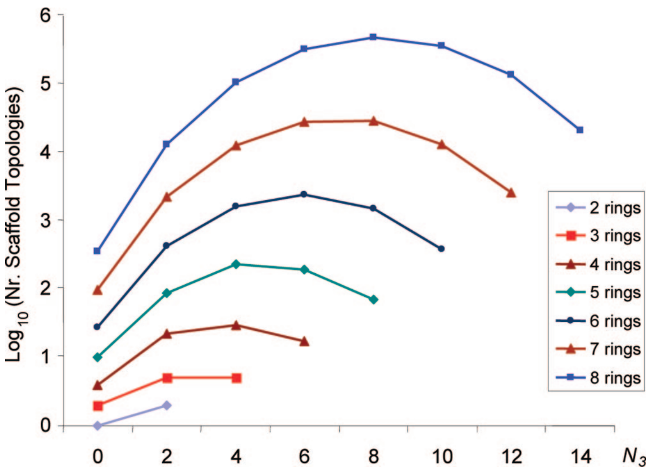


Figure 9. Total number of distinct topologies with two through eight rings, plotted as a function of N_3.

7. RESULTS AND CONCLUSIONS

In this paper, we described a method and an algorithm for the systematic generation of topologies with up to, and including, eight rings and an efficient (cubic time) algorithm for comparing these graphs to determine isomorphism. Furthermore, we produced a unique characterization for scaffold topology pseudographs with up to eight rings. A practical application of this result follows: If all small molecules (up to eight rings) in a given chemical database are tagged by the ordered return index characterizing their topologies (an operation that only needs to be performed once for any given database), then the problem of deciding if a given molecule is present in the database can be quickly reduced by querying only those database entries with the same topology. This renders database searching more efficient, in particular since most chemical collections now exceed 10^7 unique chemicals.

The total numbers of topologies in each class of (r, N_3, N_4) are summarized in Table 1 and shown in Figure 8. A lower bound for the number of unique topologies in (9, 16, 0) is 204 637. We have not confirmed whether the return index is adequate to distinguish between topologies with 9 or 10 rings, and we have found counterexamples for which the return index supplemented with only nearest neighbor loop information fails for 11 and 12 rings.

The population density of the topological scaffold space is higher at the midlevel combination of 3-nodes and 4-nodes for any given number of rings (Figure 9). The shape of the population density curves is similar to that of the binomial coefficients. This is in notable contrast to the population densities of topologies found in the chemical databases discussed in a paired paper.[3] Those chemical databases show higher populations for topologies containing not more than one 4-node.

We note that the number of possible scaffold topologies for up to six rings is slightly over 7000 and dramatically increases with higher ring numbers. Moreover, the number of nonplanar topologies grows with the number of rings: While there are no nonplanar scaffold topologies with two or three rings and exactly one with four, the number grows to roughly 10% of the total for eight rings. In an accompanying paper, we present the topological scaffold space occupancy (distribution) for a diverse set of chemical databases.[6] The probability of finding existing molecules for a given scaffold topology decreases rapidly for higher ring numbers. Additionally, there are exactly 44 molecules, belonging to 12 distinct nonplanar topology classes, found in the entire merged database we considered[6] (planarity was determined using the routine ***PLANARG*** of ***nauty***[12]).

Since this is a complete enumeration of all of the possible scaffold topologies, we anticipate that the use of this system can become standard for rapid queries of ultralarge databases. Furthermore, this system can provide a basis for the systematic topological classification of organic small molecules and serve as a first step to the complete mapping of topological chemical space.

ACKNOWLEDGMENT

We wish to thank Cristian Bologa and Tharun Kumar Allu (UNM Biocomputing) for all their help and advice. This research was funded in part by the University of New Mexico Initiative for Cross Campus Collaboration in the Biological and Life Sciences, and by the New Mexico Tobacco Settlement Fund. Canonical SMILES for each scaffold topology and semiannual updates for select chemical databases are available at the UNM Biocomputing Web site.[20]

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CI7003412