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APPLICATIONS OF ARTIFICIAL INTELLIGENCE FOR CHEMICAL INFERENCE. XII. EXHAUSTIVE GENERATION OF CYCLIC AND ACYCLIC ISOMERS

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APPLICATIONS OF ARTIFICIAL INTELLIGENCE FOR CHEMICAL INFERENCE - XII
Exhaustive Generation of Cyclic and Acyclic Isomers.[1,2]

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ABSTRACT. A systematic method of identification of all possible graph isomers consistent with a given empirical formula is described. The method, embodied in a computer program, generates a complete list of isomers. Duplicate structures are avoided prospectively.

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(1) For Part XI see R. Carhart and C. Djerassi, *J. Chem. Soc., Perkin II*, in press.

(2) Financial support for this work was provided by the National Institutes of Health (RR 00612-03) and the Advanced Research Projects Agency (SD-183).

Problems of structural isomerism in chemistry have received much attention. But only occasional inroads have been made toward a systematic solution of the underlying graph theoretical problems of structural isomerism. Solutions in the past have been partial, with acyclic and cyclic structures being treated independently. Recently the "boundaries, scope and limits"[3] of the subject of structural isomerism of acyclic molecules have been defined by the DENDRAL algorithm[3]. This algorithm permits an enumeration and representation of all possible acyclic molecular structures with a given empirical formula.

Acyclic molecules represent only a subset of molecular structures, however, and it may be argued that cyclic structures (including those possessing acyclic chains) are of more general interest and importance to modern chemistry from both a practical and theoretical standpoint. An approach to cyclic structure generation has appeared in a previous paper in this series[4]. That approach, which operates on a set of previously generated acyclic forms by labelling hydrogen atoms pairwise and connecting the atoms to which they are attached with a new bond, has one serious drawback. The approach cannot make efficient use of the symmetry properties of cyclic graphs; hence an inordinate amount of computer time must be

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(3) J. Lederberg, G.L. Sutherland, B.G. Buchanan, E.A. Feigenbaum, A.V. Robertson, A.M. Duffield, and C. Djerassi, J. Amer. Chem. Soc., 91, 2973 (1969).

(4) Y.M. Sheikh, A. Buchs, A.B. Delfino, G. Schroll, A.M. Duffield, C. Djerassi, B.G. Buchanan, G.L. Sutherland, E.A. Feigenbaum, and J. Lederberg, Org. Mass Spectrom., 4, 493 (1970).

spent in retrospective checking of each candidate structure with existing structures to remove duplicates. For this reason, an alternative approach to construction of cyclic molecules has been developed. This approach is designed to take advantage of the underlying graph theoretic considerations, primarily symmetry, to arrive at a method for more efficient construction of a complete and irredundant list of isomers for a given empirical formula. Central to the successful solution of this problem is the generation of all positional isomers obtained by substitutions on a given ring system. This topic has received attention for nearly 100 years, with limited success[5]. Its more general ramifications go far beyond organic chemistry. Graph theoreticians have considered various aspects of this topic, frequently, but not necessarily, in the context of organic molecules. Polya has presented a theorem[6] which permits calculation of the number of structural isomers for a given ring system. Hill[7a,b] has applied this theorem to enumeration of isomers of simple ring compounds and Hill[7c] and Taylor[8] have

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(5) See, for example, A.C. Lunn and J.K. Senior, *J. Phys. Chem.*, **33**, 1027 (1929) and references cited therein.

(6) a) G. Polya, *Compt. rend.*, **201**, 1167 (1935);
b) G. Polya, *Helv. Chim. Acta*, **19**, 22 (1936);
c) G. Polya, *Z. Kryst.* **93**, 415 (1936);
d) G. Polya, *Acta Math.*, **68**, 145 (1937).

(7) a) T.L. Hill, *J. Phys. Chem.*, **47**, 253 (1943);
b) T.L. Hill, *ibid.*, p. 413.
c) T.L. Hill, *J. Chem. Phys.*, **11**, 294 (1943).

(8) W.J. Taylor *J. Chem. Phys.*, **11**, 532 (1943).

pointed out that Polya's theorem permits enumeration of geometrical and optical isomers in addition to structural isomers. More recently, formulae for enumeration of isomers of monocyclic aromatic compounds based on graph theory, permutation groups and Polya's theorem have been presented[9a]. This history of interest and results provides only marginal benefit to the organic chemist. Although the number of isomers may be interesting, these methods[5-9a] do not display the structure of each isomer. Also, these methods do not provide information on the more general case where the ring system is embedded in a more complex structure. Even for simple cases the task of specifying each structure by hand, without duplication, is an onerous one.

Balaban has published a series of papers[9] addressed, in part, to the problem of specification of isomeric structures. Although his method, which differs substantially from our own, involves significant manual effort and does not appear to encompass a mechanism for prospective avoidance of duplicate structures, his compilations of isomers of annulenes[9b,9c], represent an important contribution as extensions to the compilations of Lederberg[10].

METHOD

OVERVIEW

Framework. The framework for this method is that chemical structures consist of some combination of acyclic chains and rings or ring systems[10,11]. The problem of construction of acyclic isomers

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9a) A.T. Balaban and F. Harary, Rev. Roum. Chim., 12, 1511 (1967); b) ibid., 11, 1097 (1966); Erratum, ibid., 12, No. 1, 103 (1967); c) ibid., 17, 865 (1972); d) ibid., 18, 635 (1973), and additional references cited therein.

10) J. Lederberg, DENDRAL-64, Part I. Notational Algorithm for Tree Structures, NASA Star No. N65-13158, NASA CR-57029; Part II. Topology of Cyclic Graphs, NASA Star No. N66-14074, NASA CR-68898; Part III. Complete Chemical Graphs: Embedding Rings in Trees, NASA Star No. N71-76061, NASA CR-123176.

11) It is assumed that structures are completely connected by chemical bonds; thus catenates and threaded structures are viewed as consisting of separate molecules.

(and radicals) has been solved previously[3]. If all possible ring systems can be constructed from all or part of the atoms in the empirical formula, and all possible acyclic parts are available from the acyclic generator, the combination of ring systems with acyclic parts in all unique ways would yield the complete list of isomers. The method for construction of ring systems is described below. This description employs some terms which require definition. The definitions also serve to illustrate the taxonomic principles which underlie the operation of the structure generator. The generator's view of molecular structure differs in some respects from the chemist's. A chemist, for example, may view structures possessing the same functional group or ring as related. The generator works at the more fundamental level of the vertex-graph[10], as described below.

Chemical Graph. A molecular structure may be viewed as a graph, termed the *chemical graph*, or skeleton. A chemical graph consists of *nodes*, with associated atom names, and *edges*, which correspond to chemical bonds. Consider as an example the substituted piperazine, 1, whose chemical graph is illustrated in Chart I as 2. Note that hydrogen atoms are ignored by convention, while the symbol "U" is used to specify the unsaturation. The degree (primary, secondary, ...) of a node in the chemical graph has its usual meaning, i.e., the

number of (non-hydrogen) edges connected to it. The valence of each atom determines its maximum degree in the graph. As usally displayed by chemists in planar representation, the chemical graph describes the connectivity rather than the geometric configuration of a molecular structure.

Superatom. In general, a chemical graph can be separated into cyclic and acyclic parts. Each cyclic structural sub-unit may be deemed a *superatom* possessing any number of *free valences*[12]. The chemical graph 2 arises from a combination of two carbon atoms with ring-superatom 3. Ring-superatom 3 possesses the indicated free valences to which the remaining hydrogen and two methyl radicals will be attached (Chart 1).

Ciliated Skeleton. A *ciliated skeleton* is a skeleton with free valences but without atom names. Ring-superatom 3 arises from the ciliated skeleton 4 by associating the atom names of eight carbon and two nitrogen atoms with the skeleton (Chart 1).

Cyclic Skeleton. A chemical graph whose nodes are not associated with atom names and which contains no acyclic parts and no free

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12) A free valence is a bond with an unspecified terminus. Any substructure, cyclic or not, may be treated as a superatom; however, the term, in this paper, is generally restricted to cyclic (termed ring-) superatoms.

valences is termed a *cyclic skeleton.* Ciliated skeleton 4 arises from one way of associating sixteen free valences with the nodes on the cyclic skeleton 5 (Chart 1).

Vertex-Graph. Vertex-graphs[10] are cyclic skeletons from which nodes of degree less than three have been deleted. The vertex-graph of the cyclic skeleton 5 is the regular trivalent graph[10] of two nodes, 6. Note that the remaining nodes of the cyclic skeleton 5 are of degree two. Removal of these secondary nodes from 5 while retaining the interconnections of the two tertiary nodes yields 6 (Chart 1).

As an illustration of the variety of structures which may be constructed from a given vertex-graph and empirical formula, for example, $C_{10}H_{20}N_2$, consider that graph 6 is the vertex-graph for all bicyclic ring systems (excluding spiro forms). Cyclic skeletons 7 and 8 (Chart 1), for example, may be constructed from eight secondary nodes and 6. There are many ways of associating sixteen free valences with each cyclic skeleton, resulting in a larger number of ciliated skeletons. For example, 9 and 10 arise from different allocations of sixteen free valences to 5 (Chart 1). There is only one way to associate eight carbon atoms and two nitrogen atoms with each ciliated skeleton to yield superatoms (e.g.

Chart I

Conventional Representation:

Composition = $C_{10}H_{20}N_2$

Chemical Graph:

Composition = $C_{10}N_2U_2$

Superatoms

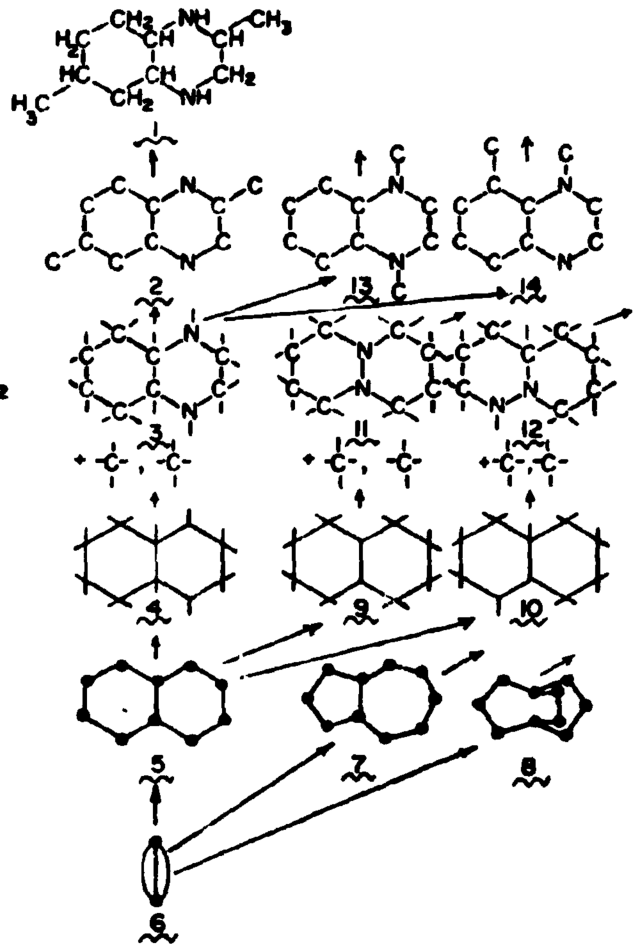
Ring-superatom Composition = $C_8N_2U_2$

Acyclic Superatom Composition = C_2

Ciliated Skeleton:

Cyclic Skeleton:

Vertex Graph



11 and 12, Chart 1). However, several structures are obtained by associating the remaining two carbon atoms (in this example) with each superatom, as an ethyl or two methyl groups. Chemical graphs 13 and 14, for example, arise from two alternative ways of associating two methyl groups with superatom 3.

Multiple Bonds. For the purposes of this program we adopt the formalism that all multiple bonds (double, triple, ...) are considered to be small rings by the program. Previous versions[3] (acyclic generator) differ from this program in that double and triple bonds are regarded as specially labelled edges.

AIMS

The structure generator must produce a complete list of structures without duplication. By duplicate structures we mean structures which are equivalent in some well-defined sense. The class of isomers generated by the program includes only connectivity isomers. Transformations (utilized to determine equivalence) allowed under connectivity symmetry preserve the valence and bond distribution of every atom. Connectivity symmetry does not consider bond lengths or bond angles. This choice of symmetry results in construction of a set of topologically unique isomers. A more detailed discussion of equivalence is discussed in Appendix A and in the accompanying paper[13] ; a discussion of isomerism and symmetry is presented in Appendix B.

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13) L. Masinter, N.S. Sridharan, J. Amer. Chem. Soc., 00, 0000 (1973).

STRATEGY

The strategy behind the cyclic structure generator is strongly tied to the framework described above. The strategy is summarized in greatly simplified form in Figure 1. The vertex-graphs from which structures are constructed can be specified for a given problem by a series of calculations. Thus Part A of the program (Figure 1) partitions the pot of atoms in all possible ways; each partition consists of those atoms assigned to one or more "superatompots" and a "remaining pot." Each superatompot is a collection of atoms from which all possible, unique ring-superatoms[12] can be constructed based on the appropriate vertex-graphs (Part B, Fig. 1). Each ring-superatom will be a ring system in completed structures. The atoms in the remaining pot will form acyclic parts of the final structures when combined in all possible, unique ways with the ring-superatoms from the corresponding initial partition (Part C, Fig. 1).

DESCRIPTION

We are faced with the difficulty of describing a complex computer program in the traditional mode of presentation in a scientific journal. The narrative form is not the ideal medium for this description; simple examples do not always indicate all essential aspects of a program. A deeper understanding of a program could be engendered through the use of a large number of well chosen examples, but the length of such a presentation would be excessive and would tax the patience of even the most interested reader.

We are thus aware of the insufficiency of considering only one example in the following written description. We have adopted the strategy of presenting essential aspects of the procedure for structure generation in the main body of the text. Details of the description which might obscure the principal concepts are placed in Appendices C and D. Mathematical details are available elsewhere.[14, 15] We hope this serves the purpose of providing the casual reader with a deeper understanding of the method without having to contend with details which, on the other hand, are important to others who wish to make use of our approach.

The example chosen to illustrate each step of the method is C_6H_8 (or C_6U_3 as there are three degrees of unsaturation).

This example does not contain bivalent or trivalent atoms (e.g., oxygen and nitrogen, respectively) or atoms of valence greater than four, nor any univalent atoms other than hydrogen (e.g., chlorine, fluorine).

Partitioning and Labelling. The mechanism for structure generation involves a series of "partitioning" steps followed by a series of

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(14) (a) H. Brown, L. Masinter and L. Hjelmeland, Discrete Mathematics, in press;
(b) Stanford Computer Science Memo STAN-CS-72-0318.

(15) (a) H. Brown and L. Masinter, Discrete Mathematics, submitted;
(b) Stanford Computer Science Memo STAN-CS-73-0361.

"labelling" steps. Partitions are made of items which must be assigned to objects (usually graph structures or parts thereof) as the molecular structures are built up from the vertex-graphs. The process by which items are assigned to the graphs is termed labelling.[13,14]

Examination of Chart I reveals the different types of items involved. For example, nodes are partitioned among and labelled upon the edges of the vertex-graphs to yield the cyclic skeletons. Free valences are partitioned among and labelled upon the nodes of cyclic skeletons to yield ciliated skeletons, and so forth.

Partitioning steps in the subsequent discussion are carried out assuming that objects among which items are partitionsd are indistinguishable. Distinguishability of objects (edges, nodes, ...) is specified during labelling and will be discussed in a subsequent section. The partitioning steps performed by the program are outlined in Table I. Each step is described in more detail below.

Table 1. Partitioning Steps Performed by the Structure Generator

Step #	Partition	Among
1	Atoms and Unsaturations in Empirical Formula	Superatompots and Remaining Pot
2	Free Valence	Atoms in Superatompot
3	Secondary Nodes	Loops / Non-loops
4	Non-loop Secondary Nodes	Edges of Graph
5	Loop Secondary Nodes	Loops
6	Ring-superatoms and Remaining Pot	Efferent Links (see Appendix D)

PART A. Superatom Partitions.

Ring-superatoms are "two-connected" structures, i.e., the ring-superatom cannot be split into two parts by scission of a single bond. The atoms in an empirical formula may be distributed among from one to several such two-connected ring-superatoms. A distribution which allots atoms to two or more superatompots will yield (respectively) structures containing two or more ring-superatoms linked together by single bonds (or acyclic chains)[16].

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16) Chemists are more familiar with terms such as rings or ring systems. The term two-connected is used here in conjunction with ring-superatoms for a more precise description. For example, biphenyl may be viewed as a single ring system or two rings depending on the chemical context. In this work, however, biphenyl consists of two ring-superatoms (two phenyl rings) linked by a single bond.

In the generation process, one must find all possible ways of partitioning the given formula into superatompots and a remaining pot, such that molecules can be constructed. The considerations in forming superatom partitions deal primarily with valence and unsaturation. This procedure is summarized in Appendix C, Superatom Partitions. The partitions which result are summarized in Table II.

Table II. Allowed Partitions of C_6U_3 Into Superatompots and Remaining Pot.

Partition Number	Number of Superatompots	Superatompot 1	Superatompot 2	Number 3	Remaining Pot
1	1	C_6U_3	-	-	-
2	1	C_5U_3	-	-	C_1
3	1	C_4U_3	-	-	C_2
4	1	C_3U_3	-	-	C_3
5	2	C_4U_2	C_2U_1	-	-
6	2	C_3U_2	C_2U_1	-	C_1
7	2	C_2U_2	C_2U_1	-	C_2
8	2	C_4U_1	C_2U_2	-	-
9	2	C_3U_1	C_2U_2	-	C_1
10	2	C_3U_2	C_3U_1	-	-
11	3	C_2U_1	C_2U_1	C_2U_1	-

PART B. Ring-superatom Construction.

Each partition (Table II) must now be treated in turn. The complete set of ring-superatoms for each superatompot in a given partition must be constructed. The major steps in the procedure are outlined in Figure 2.

Valence List. The first step in part B is to strip the superatompot of atom names, while retaining the valence of each atom. The numbers of each type of atom are saved for later labelling of the ciliated skeletons (Chart I). A valence list may then be specified, giving in order the number of bi-, tri-, tetra- and n-valent nodes which will be incorporated in the superatom. Thus the superatompot C_6U_3 is transformed into the valence list 0 bivalents, 0 trivalents, 6 tetravalents (0, 0, 6), and C_4U_2 becomes (0, 0, 4) (Figure 2).

Calculation of Free Valence. From the valence list and the associated unsaturation count the number of free valences of each superatompot is determined uniquely. (see Calculation of Free Valence, Appendix C). For C_6U_3 the free valence is eight (Fig. 2). The free valence of a superatom represents the number of bonding sites which can connect to hydrogen atoms, other superatoms or atoms in the remaining pot.

Partitioning of Free Valence. The free valences are then partitioned among the nodes in the valence list in all possible, unique ways. (see Appendix C, Partitioning of Free Valence).

Degree List. Each partition of free valences alters the effective valence of the nodes in the original valence list with respect to the ring-superatom. In the example, assignment of one or two free valences to a tetravalent node transforms this node into a tri- or bivalent node respectively. As the ring-superatom is constructed, those tetravalent nodes which have been assigned, say, two free valences, have then only two valences remaining for attachment to the ring-superatom. These nodes are then of degree[17] two and may be termed secondary nodes. Thus the partition of free valences 2,2,2,2,0,0 on six tetravalent nodes yields the degree list (4,0,2) (Fig. 2) as four of the tetravalent nodes receive two free valences each, yielding four nodes of degree two (secondary) and leaving two nodes of degree four (quaternary). The program keeps track of the number of free valences assigned to all nodes for use in a subsequent step.

Loops. As will be clarified in the subsequent discussion, there are several general types of ring-superatoms which cannot be constructed from the vertex-graphs available in the CATALOG (described below).

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17) Use of the term degree with reference to the degree list refers to the number of bonds other than free valences, with double bonds being counted twice. A free valence may or may not eventually be attached to a hydrogen atom in the final structure.

These are all cases of multiple extended unsaturations either in the form of double bonds or rings. Examples are the following:

1) bi-, tri-, ... n-cyclics with exocyclic double bonds;
2) some types of spiro ring systems;
3) allenes extended by additional double bonds, e.g.,
C=C=C=C

The concept of a loop, each loop consisting of a single unsaturation and at least one bivalent node, must be utilized for these cases. Examples of loops containing one, two and three bivalent nodes are shown in Chart II. Note that the two remaining "ends" of the unsaturation will yield a "looped structure" when attached to a single node in a graph (shown as X, Chart II).

Chart II

bivalents = 1 2 3

The method for specification of loops is discussed in Calculation of Loops, Appendix C.

Partitioning of Secondary Nodes among Loops and Non-loops. The secondary nodes in the degree list are partitioned between the loops (if any) calculated in the previous step and the remaining non-loop portion of the eventual graph.

Aspects of this partitioning step are presented in Partitioning of Secondary Nodes Among Loops and Non-Loops, Appendix C. Results for the example are indicated in Figure 2.

Reduced Degree List. This procedure yields the reduced degree list which contains none of the secondary nodes originally present in the degree list. Any secondary nodes appearing in the reduced degree list are termed "special" secondary nodes as these nodes will have loops attached in subsequent steps.

Vertex-Graphs. The reduced degree lists are used to specify a set of vertex-graphs for the eventual ring-superatoms. All two-connected structures can be described by their vertex-graphs, which are, for most structures, regular trivalent graphs. This concept has been described in detail by Lederberg[10], who has also presented a generation and classification scheme for such graphs. Given a set of all vertex-graphs, the set of all ring-superatoms may be specified[15]. The vertex-graphs are maintained by the program in the CATALOG. Catalog entries for regular trivalent graphs possessing two and four nodes are presented in Table III. This list must be supplemented by additional vertex-graphs to cover several special cases required for generation of all structures for the example. These are also presented in Table III. With the reduced degree list of a

TABLE III. Vertex-Graphs Necessary for Construction of Isomers of C_6H_8. This is a Partial Listing of the Catalog.[a]

Planar Representation	Name[b]	Number of Nodes of Degree Three	Number of Nodes of Degree Four	Remarks
	2A (hosahedron)	2	0	Regular trivalent graph of two nodes
	4AA	4	0	Regular trivalent graphs of four nodes
	4BB (tetrahedron)	4	0	
	"Singlering k"	0	0	A single ring composed of k secondary nodes
	Tetravalent Dihedron	0	2	Two nodes of degree four
	"Daisy"	0	1	A single quaternary node
	$3BCB	2	1	-

(a) The listing of reference 10 has been expanded to include vertex-graphs of other combinations of nodes of degree three and four[18a]. The completeness of the Catalog has been verified where possible by independent graph construction methods [18] and by comparison with Balaban's compilations[9b,9c] where appropriate.

(b) Names, except those in quotation marks, taken from Lederberg.[10]

18a) N.S. Sridharan, unpublished results; b) L. Masinter, unpublished results.

superatompot, the program requests the appropriate CATALOG entries. In the example (Fig. 2), the reduced degree list (0,0,2) specifies vertex-graphs containing two quaternary nodes (tetravalent dihedron). The reduced degree list (0,4,0) specifies regular trivalent graphs of four nodes, of which there are two: 4AA and 4BB (Table III). When *only* secondary nodes are present in the reduced degree list, the graph "Singlering" (Table III) is utilized.

Interlude. Up to this point the program has effectively decomposed the problem into a series of subproblems, working down from the total pot of atoms through a series of partitions and subpartitions to the set of possible vertex-graphs. In subsequent steps the vertex-graphs are expanded to the final structures by a series of constructive graph labellings (Table IV).

Table IV. The Six Graph Labelling Steps Performed by the Labelling Algorithm

Labelling Step	Function
1	Label Edges of Vertex-Graphs with Special Secondary Nodes
2	Label Edges of Resulting Graphs with Non-Loop Secondary Nodes
3	Label Loops of Resulting Graphs with Loop Secondary Nodes
4	Label Nodes of Cyclic Skeletons with Free Valences
5	Label Nodes of Ciliated Skeletons with Atom Names
6	Label Free Valences of Superatoms with Radicals (see Appendix D)

Labelling Edges of Vertex-Graphs with Special Secondary Nodes. Special secondary nodes are those that will have loops attached. The specification of the possible attachments of the nodes to the graph is a "labelling" procedure. This is the first of six such graph labelling steps performed by the program. (Table IV). All of these labelling steps involve the same combinatorial problem, that of associating a set of *n* labels, not necessarily distinct, with a set of objects with arbitrary symmetry[13]. The same labelling algorithm is utilized for each of the six labelling steps. A description of the underlying mathematics and proof of completeness and irredundancy appears separately[14].

Some aspects of the first labelling step indicate how equivalent labellings (which would eventually yield duplicate structures) may be avoided prospectively, by recognition of the symmetry properties of the graph; in the first labelling, the vertex-graph. These symmetry properties are expressed in terms of the permutation group (see Appendix A and refs. 13 and 14) on the edges of the vertex-graph. This permutation group, which defines the equivalence of the edges, may be specified in the CATALOG or, alternatively, calculated as needed by a separate part of the structure generator. As subsequent steps are executed, a new permutation group (e.g., on the nodes for labelling step four, Table IV) is derived as necessary[13]. Thus, only labellings which result in unique expansions of the structure are permitted. The reader examining Fig. 2 may note that for this simple example the symmetries of the vertex-graphs and subsequent skeletons can be discerned easily by eye. For example, all edges of the tetravalent dihedron are equivalent, as are all the edges of the regular trivalent graphs 2A and also 4BB. The $3BCB graph (Table II, Fig. 2) has four equivalent edges and one other edge, and so forth. In the general case, however, the symmetries of the vertex-graphs and subsequent expansions thereof are not always obvious.

With the group on the edges specified, the labelling of the vertex-

graphs with special secondary nodes is carried out. The results of this procedure for partitions containing loops are indicated in Figure 2.

Labelling with Non-Loop Secondary Nodes. The graphs which resulted from the previous labelling are now labelled with the partitions of non-loop secondary nodes (see Partitioning of Non-Loop Secondary Nodes Among Edges, Appendix C). Each of the five partitions for the tetravalent dihedron in Fig. 2 results in a single labelling, as all four edges of the graph are equivalent. When edges are distinguishable there may be several ways to label a graph with a single partition. There are, for example, for the $38CB graph, two ways to label with the partition 3,0,0,0,0, four ways with the partition 2,1,0,0,0 and three ways with the partition 1,1,1,0,0 (Fig. 2).

Labelling with Loop Secondary Nodes. There remain unassigned to the graphs at this point only secondary nodes which were assigned to loops. These nodes are first partitioned among the loops. (see Partitioning of Loop Secondary Nodes Among Loops, Appendix C). For example, following the path from the degree list (4,0,2) through labelling with non-loop secondary nodes (Fig. 2), there are two ways of labelling the two equivalent loops with four secondary nodes. There is one way to label the two loops of the adjacent graph with three

secondary nodes and one way of labelling the two loops of each of the two remaining graphs in this section of Figure 2 with two secondary nodes. In this example $(C_6 U_3)$ the loops in every case are equivalent or there is only one loop to be labelled. In the general case loops may not be equivalent, resulting in a greater number of ways to label loops with a given partition of secondary nodes.

Cyclic Skeletons. The previous labelling steps specified the number of secondary nodes on each edge of and loop attached to the vertex-graphs. All atoms in the original superatompot are thus accounted for. A representation of the result is the cyclic skeleton, where nodes and their connections to one another are specified. (These skeletons begin to resemble conventional chemical structures.)

Labelling with Free Valences. The nodes in a cyclic skeleton are then labelled with free valences, yielding ciliated skeletons. This labelling is trivial in the example, as all atoms are of the same valence (four) (Figure 2). Free valence labelling is performed with knowledge of how many atoms of each valence were present in the original superatompot, but independent of the *identities* of the atoms. The combinatorial complexity of this labelling problem follows from the possible occurence of atoms with differing valences. In the general case there may be several ways to perform this labelling on a

single cyclic skeleton, whereas in the C_6U_3 example there is only one way.

Labelling with Atom Names. The nodes of a ciliated skeleton are then labelled with atom names to yield the ring-superatom(s). Again this labelling is trivial in the example, as only one type of atom is present (carbon), yielding in each case only a single superatom (Fig. 2). If there is more than one type of atom with the same valence (e.g., silicon and carbon), the labelling problem is more complex. Each node of appropriate valence may be labelled with either type of atom. Duplicate structures are avoided by calculations involving the group pertaining to the set of nodes of equal valence.

PART C. Acyclic Generator.

The superatom partition expanded in the example had no atoms assigned to acyclic chains (remaining pot). The set of ring-superatoms on completion of Part B, above, thus yields the set of 36 structures on placement of a hydrogen atom on each free valence (Fig. 2). If the superatom partition (partitions 2-11, Table II) contained more than one superatompot or any atoms in the remaining pot, the acyclic generator must be used to connect the segments of the structure in all ways. This procedure is described in detail in Appendix D.

DISCUSSION

Completion of C_6H_8. The example (Fig. 2) has considered only expansion of a single superatom partition. It might be instructive for the reader to attempt to generate all, or at least the remaining, structures for C_6H_8. The number of solutions is presented in a subsequent section. If the algorithm as outlined in Figure 2 is followed, it is suggested that the initial superatom partitions in Table II be examined carefully. These partitions yield some indication of the types of structures which will result from each partition. For example, partition 4, C_3U_3 in a single superatompot, plus three carbons in the remaining pot, should yield all structures containing a three-membered ring possessing two double bonds or a triple bond. As there are only two free valences, the remaining atoms can be in a single chain (as a propyl or iso-propyl radical) or as a methyl and an ethyl group, but not as three methyl groups.

Completeness and Irredundancy. Although a mathematical proof of the completeness and irredundancy of the method exists[15], there is no guarantee that the implementation of the algorithm in a computer program maintains these desired characteristics. Confidence in the completeness and irredundancy of a program of this complexity can be engendered in the following ways:

1) Verification of the program's performance by another, completely independent approach. An independent method has been developed which enumerates, but does not construct, all isomers of compositions containing C,H,N, and O[18b]. It is interesting that the program for simple counting of the solutions is significantly slower than construction of all of the solutions, despite some effort to improve the efficiency of the former program. Thus, due to limitations of computer time, we have been limited to compositions containing only 5 or fewer non-hydrogen atoms. For these cases, however, the numbers of isomers obtained by both programs agree.

Balaban has presented lists of isomers of C_4H_4, C_6H_6, C_5H_8 and C_4H_4O[9d]. These lists were derived from his tables[9d] of graphs of degrees 2-4 and orders (numbers of nodes) 1-5. Although we agree with his lists of hydrocarbon isomers, the list of isomers of C_4H_4O is incomplete. The structure generator provides 62 structures (as opposed to 59). The three missing structures are:

These structures should have been produced following Balaban's method[9d]. The fact that they were not points out the difficulties inherent in any procedure for isomer generation in which manual steps are involved (see below).

2) Testing by manual generation of structures. Several chemists, all without knowledge of the algorithm described above, have been given several test cases, including C_6U_3, from which structures were generated by hand. Familiarity with chemistry is no guarantee of success, as evidenced by the performance of three chemists for the superficially simple case of C_6U_3 (C_6H_8, Table V).

Table V. Performance of Three* Chemists in Manual Generation of Isomers of C_6H_8 (C_6U_3). There are 159 Isomers.

	Number Generated	Type of Error
Chemist 1	161	4 duplicates; 4 omissions 2 with 7 carbon atoms.
Chemist 2	168	16 duplicates; 7 omissions
Chemist 3	160	2 duplicates; 1 omission

* One PhD and two graduate students.

This example indicates that for more than very trivial cases, it is extremely difficult to avoid duplicates (tricyclics, for example, are difficult to visualize when testing for duplicates) and omissions. Omissions appear to result from both carelessness and neglect of ring systems that are implausible or unfamiliar. The program seems better at testing the chemist than vice versa. In every instance of manual structure generation, no one has been able to construct a legal structure that the program failed to construct. No one has been able to detect an instance of duplication by the program. This performance builds some confidence, but manual verification of more complicated cases is extremely tedious and difficult. Isomers for many empirical formulae have been generated, and some results are tabulated in Table VI. The choice of examples

has been motivated by a desire to test all parts of the program where errors may exist while keeping the number of isomers small enough to allow verification. In this manner all obvious sources of error have been checked, for example, construction of loops on loops, multiple types of atoms of the same valence (e.g., Cl, Br, I) and examples containing atoms of several different valences including penta- and hexavalent atoms.

3) Varying the order of generation. The structure of the program permits additional tests by doing some operations in a different order. For example, one variation allowed is to leave hydrogens associated with the atoms in each partition rather than to strip them away initially and place them on the remaining free valences in the last step. Each such test has resulted in the same set of isomers.

4) Using Polya enumeration[6] at the various labelling steps of the procedure to verify the correctness of sub-parts of the program. Using various combinatorial formulae, one can insure that the results of at least parts of the program are consistent with independent calculations. This approach was used extensively in the development of the labelling algorithm.

In summary, the verification procedures utilized have all indicated absence of errors in the computer implementation of the algorithm. Also, there is no clear reason why generation of larger sets of isomers should not also proceed correctly. The final verdict however, must await development of new mathematical tools for verification by enumeration (see above) or an alternative algorithm.

Table VI. The Number of Isomers for Several Empirical Formulae

Empirical Formula	Example Compound	Number of Isomers	Manually Verified?
C_6H_6	benzene	217	yes
C_6H_8	1,3-cyclohexadiene	159	yes
C_6H_{10}	cyclohexene	77	yes
C_6H_{12}	cyclohexane	25	yes
C_6H_{14}	hexane	5	yes
C_6H_6O	phenol	2237	no
$C_6H_{10}O$	cyclohexanone	747	no
$C_6H_{12}O$	2-hexanone	211	yes
$C_3H_4N_2$	pyrazole	155	no
$C_3H_6N_2$	2-pyrazoline	136	yes
$C_3H_8N_2$	tetrahydropyrazole	62	no
$C_3H_{10}N_2$	propylenediamine	14	yes
C_4H_9P	(pentavalent P)	110	no

Constraints. The structure generator is designed to produce a list of all possible graph isomers (Appendix B). This list contains many structures whose existence seems unlikely based on present chemical knowledge. In addition, the program may be called on to generate possible structures for an unknown in the presence of a body of data on the unknown which specify various features, e.g., functional groups) of the molecule. In such instances mechanisms are required for constraining the generator to produce only structures conforming to specified rules. The implementation of the acyclic generator possessed such a mechanism in the form of GOODLIST (desired features) and BADLIST (unwanted features)[3] which could be utilized during the course of structure generation.

The complete structure generator is less tractable. As in prospective avoidance of duplicate structures, it is important that unwanted structures, or portions thereof, be filtered out as early in the generation process as possible. It is relatively easy to specify certain general types of constraints in chemical terms, for example, the number of each of various types of rings or ring systems in the final structure, ring fusions, functional groups, substructures and so forth. It is not always so easy to devise an efficient scheme for utilizing a constraint in the algorithm, however. As seen in the above example (Fig. 2) the expanded superatom partition results in what would be viewed by the chemist as several very different ring systems.

The design of the program facilitates some types of constraints. For example, the program may be entered at the level of combining superatoms to generate structures from a set of known sub-structures. If additional atoms are present in an unknown configuration, they can be treated as a separate generation problem, the results of which are finally combined in all ways with the known superatoms. This approach will not form additional two-connected structures, however. Constraints which disallow an entire partition may be easily included. For example, it is possible to generate only pure ring isomers by "turning off" the appropriate initial superatom partitions.

Much additional work remains, however, before a reasonably complete set of constraints can be included. The implementation of each type of constraint must be examined and tested in detail to ensure that the generator remains thorough and irredundant.

CONCLUSIONS

The algorithm summarized in this paper permits the substantial realization of the graphical structures that constitute the domain of organic chemistry. The version of the algorithm presented here ignores the tetrahedral symmetry of the valences of the carbon atom. However, the topological framework readily admits of systematic tests for asymmetric centers which can then be assigned to the dichotomous categories of the alternating group A_4. This

framework also provides a simple, systematic weighting of radicals for assignment of precedence that proves to be, if anything, even more straightforward, comprehensive and free from ambiguity than the Cahn-Ingold-Prelog conventions[19].

The mathetmatical framework of our analysis is a mapping of chemical bonds onto the edges of topological graphs. This simplification can lead to disparities, for example in the description of coordination complexes, the bonds of which are non-equivalent. The symmetries of such complexes are similar to those of certain superatoms, suggesting an obvious and easy way to extend the system. Likewise, the system does not now accommodate isomerism based on steric hindrance, or the association of molecules by secondary forces, or by non-covalent constrants. For example, from a topological standpoint, threaded molecules, or catenanes, are disjoint graphs. Nor do we attempt to display the geometric conformations of molecules: indeed, some topologically plausible structures may be chemically unrealizable.

Conversely, implausible constructs, such as carbon atoms possessing "inverted" tetrahedral geometry[20] may become reality by empirical discovery. The constraints on chemically plausible structures depend on

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(19) R. S. Cahn, C. K. Ingold, and V. Prelog, Angew. Chem. Internat. Ed., 5, 385 (1966).

(20) (a) K. B. Wiberg and G. J. Burgmaier, J. Amer. Chem. Soc., 94, 7396 (1972);
(b) K. B. Wiberg, G. J. Burgmaier, K. Shen, S. J. LaPlaca, W. C. Hamilton, and M. D. Newton, J. Amer. Chem. Soc., 94, 7402 (1972).

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the domain specified by the chemist. A DENDRAL[3] system for molecular structure elucidation[25] (based on the structure generator described in this work) of molecules in frozen hydrogen matrices would have different constraints from a version useful to biochemists.

Chemists hitherto have been able to explore the de facto boundaries of their domain without explicit maps. The exhaustive and efficient study of all possible structures can now be facilitated with the assistance of computer programs that can help assure that no possible construction has been overlooked[21].

ACKNOWLEDGEMENTS

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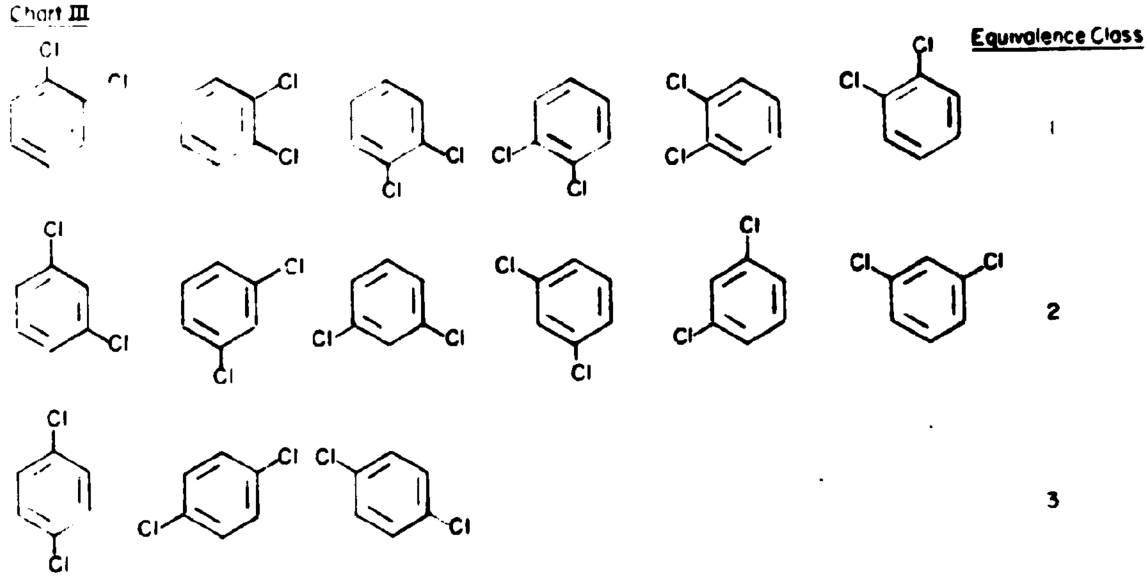
(21) (a) L. A. Paquette, S. Kirschner, and J. R. Malpass, J. Amer. Chem. Soc., 92, 4330 (1970);
(b) S. Masamune and N. Darby, Acc. Chem. Res., 5, 272 (1972);
(c) E. L. Allred and B. R. Beck, J. Amer. Chem. Soc., 95, 2393 (1973).
(d) L. T. Scott and M. Jones, Jr., Chem. Rev., 72, 181 (1972).

Appendix A. Equivalence Classes and Finite Permutation Groups.

Two members of a set of possible isomers may be defined to be equivalent if a specified transformation of one member causes it to be superimposable upon another member of the set. For example, there are fifteen possible ways of attaching two chlorine and four hydrogen atoms to a benzene ring (Chart III).

Chart III



If rotations by multiples of 60 degrees are specified as allowed transformations, the fifteen structures fall logically into three classes, termed "equivalence classes" (Chart III). Within each equivalence class structures may be made superimposable by the rotational transformation. If one element (in this case a molecular structure) is chosen from each equivalence class, the complete set of

possible structures is determined, without duplication. It is the task of the labelling algorithm to produce one and only one graph labelling corresponding to one member of each equivalence class.

The set of transformations which define an equivalence class is termed a "finite permutation group." This permutation group may be calculated based on the symmetry properties of a graph (or chemical structure in the example of Chart III). This calculation provides the mechanism for prospective avoidance of duplication. These procedures are described more fully in the accompanying paper[13].

Appendix B. Isomerism and Symmetry.

Appendix A introduced the concept of equivalence classes and finite permutation groups. The selection of transformation (Appendix A) directs the calculation of the permutation group and thus defines the equivalence classes. Different types of transformation may be allowed depending on the symmetry properties of the class of isomers considered. This Appendix discusses several of the possible types of isomerism, most of which are familiar to chemists. The reader seeking a more thorough discussion of some types of isomerism discussed below is referred to an exposition of molecular symmetry in the context of chemistry and mathematics.[22]

Isomers are most often defined as chemical structures possessing the same empirical formula. Different concepts of symmetry give rise to different classes of isomers, some of which are described below.

Permutational Isomers. Permutational isomers are isomers which have in common the same skeleton and set of ligands. They differ in the distribution of ligands about the skeleton. Gillespie et al.[23] and Klemperer[24] have used the concept of permutational isomers to probe into unimolecular rearrangement or isomerization reactions.

Stereoisomers. Ugi et al.[22] have defined the "chemical constitution" of an atom to be its bonds and bonded neighbors. Those permutational isomers which differ only by permutations of ligands at constitutionally equivalent positions form the class of stereoisomers.

Isomers Under Rigid Molecular Symmetry. If one perceives molecular structures as having rigid skeletons, the physical rotational (three dimensional) symmetries and transformations may be readily defined. Each transformation causes each atom (and bond) to

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(22) I. Ugi, D. Marquarding, H. Klusacek, G. Gokel, and P. Gillespie, *Angew. Chem. internat. Edit.*, **9**, 703 (1970).

(23) P. Gillespie, P. Hoffman, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem. internat. Edit.*, **10**, 687 (1971).

(24) (a) W. G. Klemperer, *J. Amer. Chem. Soc.*, **94**, 6948 (1972);
(b) W. G. Klemperer, *ibid.* p. 8368;
(c) W. G. Klemperer, ibid, **95**, 380 (1973);
(d) W. G. Klemperer, ibid, p. 2105.

occupy the position of another or same atom (and bond) so that the rotated structure can physically occupy its former position and at the same time be indistinguishable from it in any way. This is the most familiar form of symmetry. Under this type of symmetry conformers are distinguishable and belong in distinct equivalence classes. Every transformation is orthogonal and preserves bond angles and bond lengths as well as maintaining true chirality.

If one allows other orthogonal transformations that alter chiral properties of structures, equivalence classes result that treat both the left-handed and right-handed forms of chiral molecules to be the "same". Thus a "mirror image" transformation when suitably defined permits the left-handed form to exactly superimpose the right-handed form and vice versa.

Isomers Under Total Molecular Symmetry. If in addition to the above mentioned rigid molecular transformations one recognizes the flexional movements of a nonrigid skeleton, a dynamic symmetry group may be defined. Under this definition, different conformers now are grouped together. Thus the "chair" and "boat" conformations of cyclohexane belong to the same equivalence class under dynamic symmetry. The permutation group of skeletal flexibility is computable separately and independently of rigid molecular symmetry. One can then view total molecular symmetry as the product of the two finite permutation groups.

Isomers Under Connectivity Symmetry. The concept of connectivity symmetry was introduced previously (METHOD section). Every permutation of atoms and bonds onto themselves is a symmetry transformation for connectivity symmetry if,

a) each atom is mapped into another of like species, e.g., N to N, C to C, O to O, and

b) for every pair of atoms, the connectivity (none, single, double , triple, ...) is preserved in the mapping, i.e. the the connectivity of the two atoms is identical to the connectivity of the atoms they are mapped into.

One can readily recognize that transformations as defined automatically preserve the valence and bond distribution of every

atom. It is very probable that readers accustomed to three dimensional rotational and reflectional symmetries will tend to equate them with the symmetries of connectivity. It is emphasized again that connectivity symmetry does not consider bond lengths or bond angles, and it includes certain transformations that are conceivable but have no physical interpretation save that of permuting the atoms and bonds.

Appendix C

Superatom Partitions. The first step is to replace the hydrogen count with the degree of unsaturation. The number of unsaturations (rings plus double bonds) is determined from the empirical formula in the normal way, as given in equation 1.

$$U = 1/2\ (2+\sum_{i=1}^{n} (i-2)a_i) \qquad (1)$$

U = unsaturation
i = valence
n = maximum valence in composition
a_i = number of atoms with valence i

If the unsaturation count is zero, the formula is passed immediately to the acyclic generator. Specifying the unsaturations as U's, the example C_6H_8 becomes C_6U_3 (hydrogen atoms are omitted by convention).

There are several rules which are used during the partitioning scheme, as follows:

I. The resulting formula is stripped of other univalent atoms (e.g., chlorine) as such atoms cannot be part of two-connected ring-superatoms. These univalent atoms are relegated to the pot of remaining atoms.

II. The remaining pot in a given partition (those atoms not allocated to superatompots) can contain no unsaturations. Thus all rings and/or multiple bonds will be generated from the superatompots.

III. It follows that every superatompot in the partition must contain at least two atoms of valence two or higher plus at least one unsaturation. If there are no unsaturations then no rings could be built. In addition, an unsaturation cannot be placed on a single atom. This rule defines the minimum number of atoms and unsaturations in a superatompot.

IV. The maximum number of unsaturations in a superatompot is given by Equation 2. Superatoms must possess at least one free valence[12], so that superatompots with no free valences, e.g., O_2U_1 or C_2U_3, are not allowed, unless the superatompot contains all atoms in the empirical formula (since no univalents, and thus no hydrogens, are allowed in a superatompot, this is indeed a rare occurance.)

$$U_{max} = 1/2 \left(\sum_{i=3}^{n} (i-2)a_i\right) \qquad (2)$$

U_{max} = maximum unsaturation of a superatompot

n = maximum valence in composition

i = valence

a_i = number of atoms with valence i

V. The maximum number of superatompots for a given formula is defined by equation 3.

$$S_{max} = 1/2 \sum_{i=2}^{n} a_i \qquad (3)$$

n = maximum valence in composition

S_{max} = maximum number of superatompots in a superatom partition

a_i = number of atoms with valence i

note: the summation is over all atoms of valence $\rangle$ 2; univalents are not considered.

Rules I-V define the allowed partitions of a group of atoms into superatompots. These rules do not, however, prevent generation of equivalent partitions, which would eventually result in duplicate structures. By defining a canonical ordering scheme to govern partitioning, we prevent equivalent partitions. One such canonical ordering is as follows:

Canonical Ordering for Partitioning.

a. Partition in order of increasing number of superatompots.

b. For each entry in each part of (a), partition in order of decreasing size of superatompot by allocation of atoms one at a time to the remaining pot.

c. Each individual partition containing two or more superatompots must be in order of equal or decreasing size of the superatompot. In other words, the number of atoms and unsaturations in superatompot $\underline{n+1}$ must be equal to or less than the number in superatompart $\underline{n}$. The program notes the equality of superatompots in a partition to avoid repetition.

The application of rules I-V is best illustrated through reference to the example of C_6U_3. The maximum number of superatompots for this example is three (Equation 3). There is one way to partition C_6U_3 into one superatompot with no remaining pot, partition 1, Table II. Subsequent assignment of carbon atoms one at a time to the remaining pot results in partitions 2-4, Table II. The next partition following the sequence 1-4 would be C_2U_3 with C_4 assigned to the remaining pot. This partition is forbidden as C_2U_3 has no free valences. The three ways to partition C_6U_3 into two superatompots are indicated along with the corresponding partitions following assignment of atoms to the remaining pot, as partitions 5-10, Table II. There is only one unique way of partitioning C_6U_3 into three superatompots, partition 11, Table II.

<u>Calculation of Free Valence.</u> The expression for the free valence of a superatompot is given by equation 4.

$$FV = (2 + \sum_{i=3}^{n} (i-2)a_i) - 2U \qquad (4)$$

U = unsaturation of superatompot
i = valence
n = maximum valence in composition
a_i = number of atoms with valence i
FV = free valence

Partitioning of Free Valence. Because ring-superatoms are two-connected structures two valences of each atom of a superatompot must be used to connect the atom to the ring-superatom. Thus no free valences can be assigned to bivalent nodes in the valence list, a maximum of one to each trivalent, a maximum of two to each tetravalent, and so forth. The example (Fig. 2) is further simplified in that there are only tetravalent nodes in the valence list. Inclusion of trivalent nodes (e.g., nitrogen atoms) merely extends the number of possible partitions. The free valences are partitioned among the tetravalent nodes in all ways, as illustrated in Figure 2. It is important to note that removal of atom names makes all n-valent (n=2 or 3 or ...) nodes in the valence list equivalent at this stage. Thus the partitions (of eight free valences among six tetravalent nodes) 222200, 222020, 222002, ..., 002222 are all equivalent. Only one of these partitions is considered to avoid eventual duplication of structures.

Calculation of Loops. There are several rules which must be followed in consideration of loop assignment to ring-superatoms. The minimum (MINLOOPS) and maximum (MAXLOOPS) numbers of loops for a given valence list are designated by equations 5 and 6.

$$\text{MINLOOPS} = \max\{0\,,\ a_2 + 1/2(2n - \sum_{j=2}^{n} j a_j)\} \tag{5}$$

$$\text{MAXLOOPS} = \min\{a_2\,,\ 1/2 \sum_{j=4}^{n} (j-2)\, a_j\} \tag{6}$$

MINLOOPS = minimum number of loops
MAXLOOPS = maximum number of loops
a_j = number of nodes with degree j
j = degree
n = highest degree in list ($a_n \neq 0$)

The form of the equations results from the following considerations:

1) Only secondary nodes may be assigned to loops. Nodes of

higher degree will always be in the non-loop portion of the ring-superatom.

2) A loop, by definition, must be attached by two bonds to a single node in the resulting ring-superatom. The loop cannot be attached through the free valences. Thus the degree list must possess a sufficient number of quaternary or higher degree nodes to support the loop(s).

3) Each loop must have at least one secondary node, which is the reason MAXLOOPS is restricted to be at most the number of secondary nodes in the degree list (Equation 6).

4) There must be available one unsaturation for each loop (this is implicit in the calculation of MINLOOPS and MAXLOOPS) as each loop effectively forms a new ring.

Partitioning of Secondary Nodes between Loops and Non-Loops. For each of the possible numbers of loops (0, 1, ...) the secondary nodes are removed from the degree list and partitioned among the loops, remembering that the loops are at present indistinguishable and each loop must receive at least one secondary node. In the example (Fig. 2), starting with the degree list (4, 0, 2), there are three ways of partitioning the four secondary nodes among two loops and the remaining non-loop portion. Removal of the four secondary nodes from the degree list and assignment of two, three or four of them to two loops results in the list specified in Figure 2 as the "reduced degree list". Specification of two loops transforms the two quaternary nodes in the degree list into two secondary nodes. This results from the fact that two valences of a quaternary or higher degree node must be used to support each loop. These are "special" secondary (or higher, for atoms with valence $>$ 4) nodes, however, as these particular nodes will have loops attached as the structure is built up. Thus, in the example, any secondary nodes which are found in the reduced degree list will have a loop attached in a subsequent step. The degree list (4, 0, 2) thus becomes the reduced degree list (2, 0, 0) in the partition specifying two loops (Fig. 2). Similarly, the partition of one loop for the degree list (3, 2, 1) results in a reduced degree list of (1, 2, 0) with the three original secondary nodes partitioned among loop and non-loop portions (Figure 2).

If, after the first, second, ... nth loop partition, there remain one

or more quaternary or higher degree nodes in the reduced degree list, the list must be tested again for the possibility of additional loops. Each loop partition will result in an additional set of structures. The second pass will yield those structures possessing loops on loops, and so forth. One such superatom which would be generated in this manner from a composition of (at least) C_6U_5 is 15.

C=C=C=C=C=C
15

Partitioning of Non-Loop Secondary Nodes among Edges. The secondary nodes which were not assigned to loops ("non-loop secondary nodes") are partitioned among the edges of the graphs after labelling with special secondary nodes, or loops. Loops are not counted as edges. There are, for example, five ways to partition four non-loop secondary nodes among the edges of the vertex-graph possessing two quaternary nodes (Fig. 2).

Partitioning of Loop Secondary Nodes among Loops. This partitioning step is carried out assuming indistinguishability of the loops. Each loop must receive at least one secondary node, which limits the number of possible partitions. Results are presented in Figure 2.

Appendix D - Acyclic generator

A method of construction of structures similar to the method for acyclic isomers is utilized to join multiple ring-superatoms and remaining atoms. The DENDRAL algorithm for construction of acyclic isomers[3, 10, 25] relied on the existence of a unique central atom (or bond) to every molecule. The present acyclic generator uses the same idea. The present algorithm, though simpler in not having to treat interconnection of atoms or ring-superatoms through multiple bonds, is more complex because of the necessity to deal with the symmetries of the ring-superatoms.

D1. Method for the case with even number of total atoms.

The superatom partition $C_2U_2/C_2U_1/-/C_2$ (partition 7, Table II and Figure 2) will be used here to illustrate this procedure. The superatompots C_2U_2 and C_2U_1 have exactly one possible ring-superatom for each (see Table VII).

Table VII.

Superatompot	Superatom
C_2U_2	-C≡C-
C_2U_1	>C=C<

Thus acyclic structures are to be built with -C≡C- , >C=C< and two C's.

There are an even number of atoms and ring-superatoms. The structures to be generated fall into two categories: (a) those with bond centroid; (b) those with an atom centroid.[25]

(25) B. G. Buchanan, A. M. Duffield, and A. V. Robertson, in "Mass spectrometry, Techniques and Applications," G. W. A. Milne, ed., John Wiley and Sons, Inc., 1971, p. 121.

Category A. BOND CENTROID (see Fig. 3)

Step 1. Partition into Two Parts.

The atoms and ring-superatoms in the list of superatoms are partitioned into two parts, with each part having exactly half the total number of items. Each atom or ring-superatom is a single item. Each part has to satisfy equation 7, called the Restriction on Univalents.

Restriction on Univalents:

$$a_1 \leq [\sum_{i=2}^{n} (i-2)a_i] - 1 \qquad (7)$$

i = valence.
a_i = number of atoms or superatoms of valence i.
n = maximum valence in composition.

There are two ways of partitioning the four items into two parts (Fig. 3). The restriction on univalents is satisfied in each case. The restriction will disallow certain partitions that have "too many"[26] univalents other than hydrogens and therefore is essential only in partitioning compositions that contain any number of non-hydrogen univalents.

Step 2. Generate Radicals from Each Part.

Using a procedure described in Section D3, radicals are generated from each part in each partition. The result of application of this procedure to the example is shown in Table VIII.

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(26) The form of equation 7 results from the fact that the number of univalents (a_i) cannot exceed the number of free valences necessary to connect the superatoms, leaving one valence free for the radical valence.

Table VIII. Radicals Generated from Given Parts

Part		Radicals
(1a) -C≡C- , ⟩C=C⟨	→	-C≡C-CH=CH_2
		-CH=CH-C≡CH
		-C(=CH_2)-C≡CH
(1b) C_2	→	-CH_2-CH_3
(2a) -C≡C- , C	→	-C≡C-CH_3
		-CH_2-C≡CH
(2b) ⟩C=C⟨ , C	→	-CH=CH-CH_3
		-C(=CH_2)-CH_3
		-CH_2-CH=CH_2

Step 3. Form Molecules From Radicals.

The radicals are combined in unique pairs, within each initial partition. Each pair gives rise to a unique molecule, for each of which the centroid is a bond. There are nine such molecules for the example chosen (Fig. 3).

Category B. ATOM CENTROID (see Fig. 4).

Step 1. Selection of Centroid.

One must consider every unique atom or ring-superatom that has a free valence of three or higher as an atom centroid [10,25]. In the example, of three candidates available: -C≡C- , ⟩C=C⟨ and C, the first is not chosen for it has a free valence of only two.

Step 2. Partition the Rest of the Atoms.

The atom or ring-superatom chosen for the centroid is removed from the set and the rest are partitioned into a number of parts less than or equal to the valence of the central atom. Each part must have less than half the total number of items being partitioned (again a ring-superatom is a single item). Each part must satisfy the restriction on univalents (equation 7).

Thus, for the case where a carbon is the centroid, four partitions are attempted. The condition that each part has less than or equal to one-half the number of superatoms remaining after selection of the central atom must be satisfied, or at most one for this example. There is exactly one partition for three parts, i.e., one in each. The partitions are shown in Figure 4.

Step 3. Generate Radicals.

Once again, using the procedure described in Section D3, radicals are constructed for each part in each partition. For example, the partition -C≡C- gives rise to exactly one possible radical -C≡CH (Fig. 4).

Step 4. Combine Radicals.

Although in the example shown every part generates only one radical, in the general case there will be many radicals for each part. If so, the radicals must be combined to give all unique combinations of radicals within each part.

Step 5. Form Molecules from Central Atom and Radicals.
If the centroid is not a ring-superatom but is a simple atom, then each combination of radicals derived in Step 4 defines a single molecule that is unique. Thus for example when C is chosen as the centroid, step 4 gives one combination of radicals which determines a single molecule when connected to the central C (see Figure 4).

If the centroid is a ring-superatom and the valences of the ring-superatom are not identical then different ways of distributing the radicals around the center may yield different molecules. Labelling of the free valences of the central ring-superatom with radicals treated as labels (supplemented with adequate number of hydrogens to make up the total free valence of the ring-superatom) generates a complete and irredundant list of molecules. Thus $>C{=}C<$ is labelled with the label set:

one of $-C{\equiv}CH$, two of $-CH_3$, and one of $-H$.

There are two unique labellings as shown in Figure 4.

D2. Method for odd number of total atoms.

With an odd number of total atoms, no structures can be generated with a bond centroid. Only atom centroids are possible [10,25]. However, it is possible for structures to be built with a bivalent atom at the centroid. Thus the procedure outlined in Category B above is followed, in this case also allowing a bivalent atom as the centroid.

D3. Generation of Radicals.

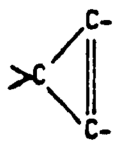
The goal of this procedure is to generate all radicals from a list of atoms and ring-superatoms. A radical is defined to be an atom or superatom with a single free valence. When a composition of atoms and ring-superatoms is presented, from which radicals are to be constructed, two special cases are recognized.

Special Case 1. Only One Atom in List of Atoms.
When only one atom which is not a ring-superatom is in the list, only one radical is possible. For example, with one C, the radical $-CH_3$ is the only possibility.

Special Case 2. Only One Ring-superatom in List of Ring-superatoms.

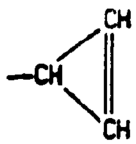
In this case, depending upon the symmetry of the ring-superatom, several radicals may be possible. This is determined by labelling the free valences of the ring-superatom with one label of a special type, a "radical-valence".

Example: A list of ring-superatoms consists of one ring-superatom, 16.

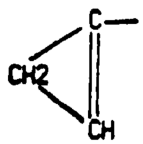


16

Two radicals result from labelling with one radical valence.



17



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General Case

Radicals have uniquely defined centroids as well [10,25]. The centroid is always an atom of valence two or higher. The steps for construction of radicals are as follows.

Step 1. Selection of Atom Centroid.

Any bivalent or higher valent atom or ring-superatom is a valid candidate to be the centroid of a radical. Thus, for example, for the composition -C≡C-, >C=C< (see part 1a in Figure 3) both are valid centroids (Figure 5).

Step 2. Partition the Rest of the Atoms.
The atom chosen for the centroid is removed from the list of superatoms. One of the valences of the centroid is to remain free (the radical valence). Therefore, the rest of the atoms in the list are partitioned into less than or equal to (valence of centroid - 1) parts. Of course, each part should satisfy the restriction on univalents (equation 7) but for constructing radicals there is no restriction on the size of the parts.

Step 3. Form Radicals from Each Part.
The procedure to construct radicals is freshly invoked on each part thus generating radicals. Each part in Figure 5 gives rise to only one radical, each arising from special case 2.

Step 4. Combine Radicals in Each Part.
For the example in Figure 5, each part yields only one radical. In a more general situation, where the rest of the list of superatoms after selection of a centroid is partitioned into several parts, and where each part yields several radicals, the radicals are combined to determine all unique combinations of radicals.

Step 5. Label Central Atom with Radicals.
If the center is an atom (not a ring-superatom) then each unique combination defines a single unique molecule.

If the center is a ring-superatom, the radicals are determined by labelling the center with a set of labels which includes: i) the radicals; ii) a leading radical-valence; iii) an adequate number of hydrogens to make up the remaining free valences of the ring-superatom. One selection of center gives one radical and the other gives two more, to complete a list of three radicals for the example chosen (Fig. 5).

Summary

For the example chosen to illustrate the operation of the acyclic generator, twelve isomers are generated, nine shown in Figure 3 and three shown in Figure 4.

FIGURE CAPTIONS

Figure 1. Outline of the strategy for structure generation.

Figure 2. Major steps in the generation of isomers as illustrated for C_6H_8. This example outlines the method for one superatom partition, that which allocates all atoms to a single superatompot with no atoms in the remaining pot.

Figure 3. Operation of the acyclic generator for the case of a bond as a centroid for the structures.

Figure 4. Operation of the acyclic generator for the case of an atom or superatom as a centroid for the structures.

Figure 5. Outline of the method for generation of radicals which are eventually combined by the acyclic generator to yield final structures.

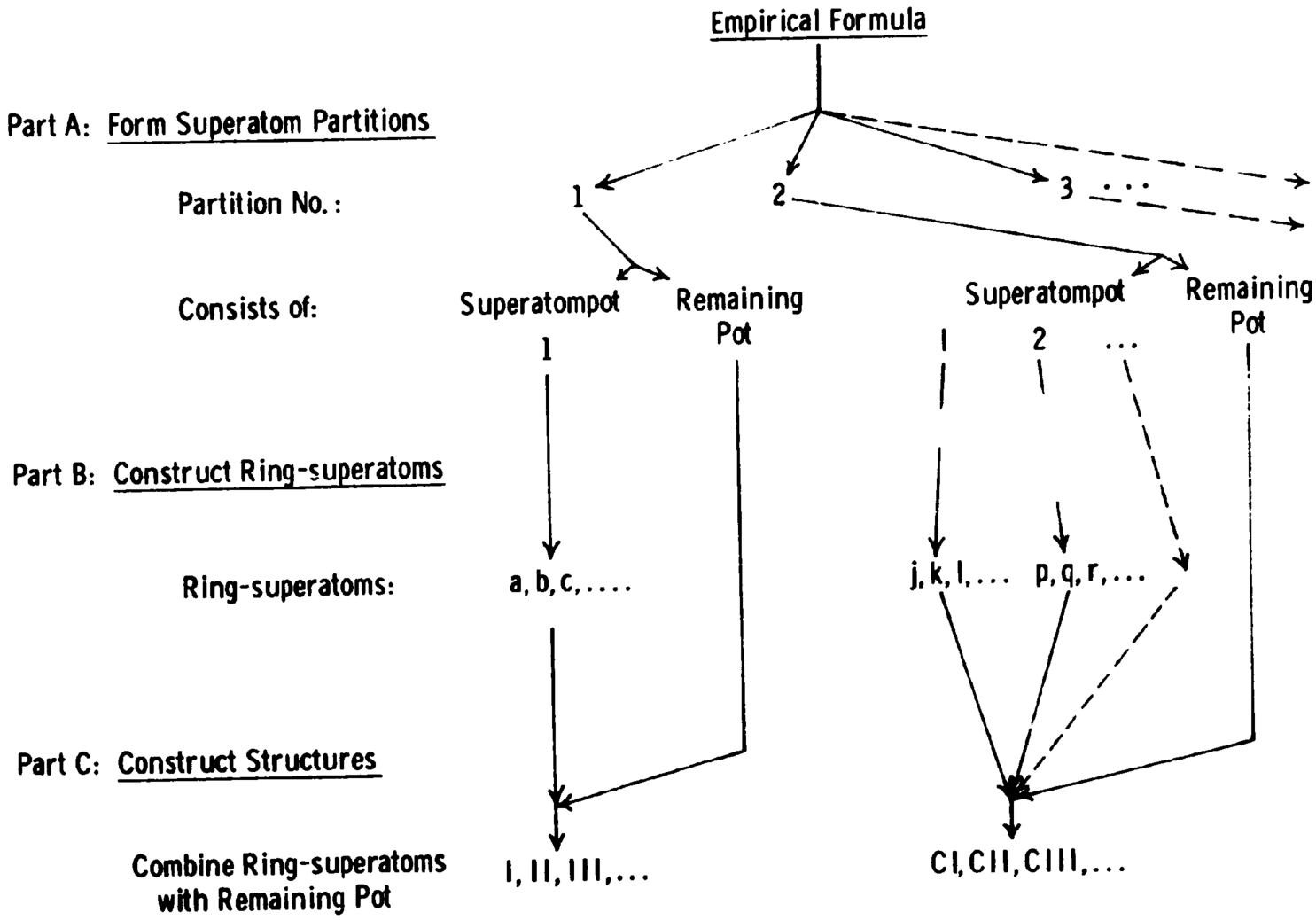
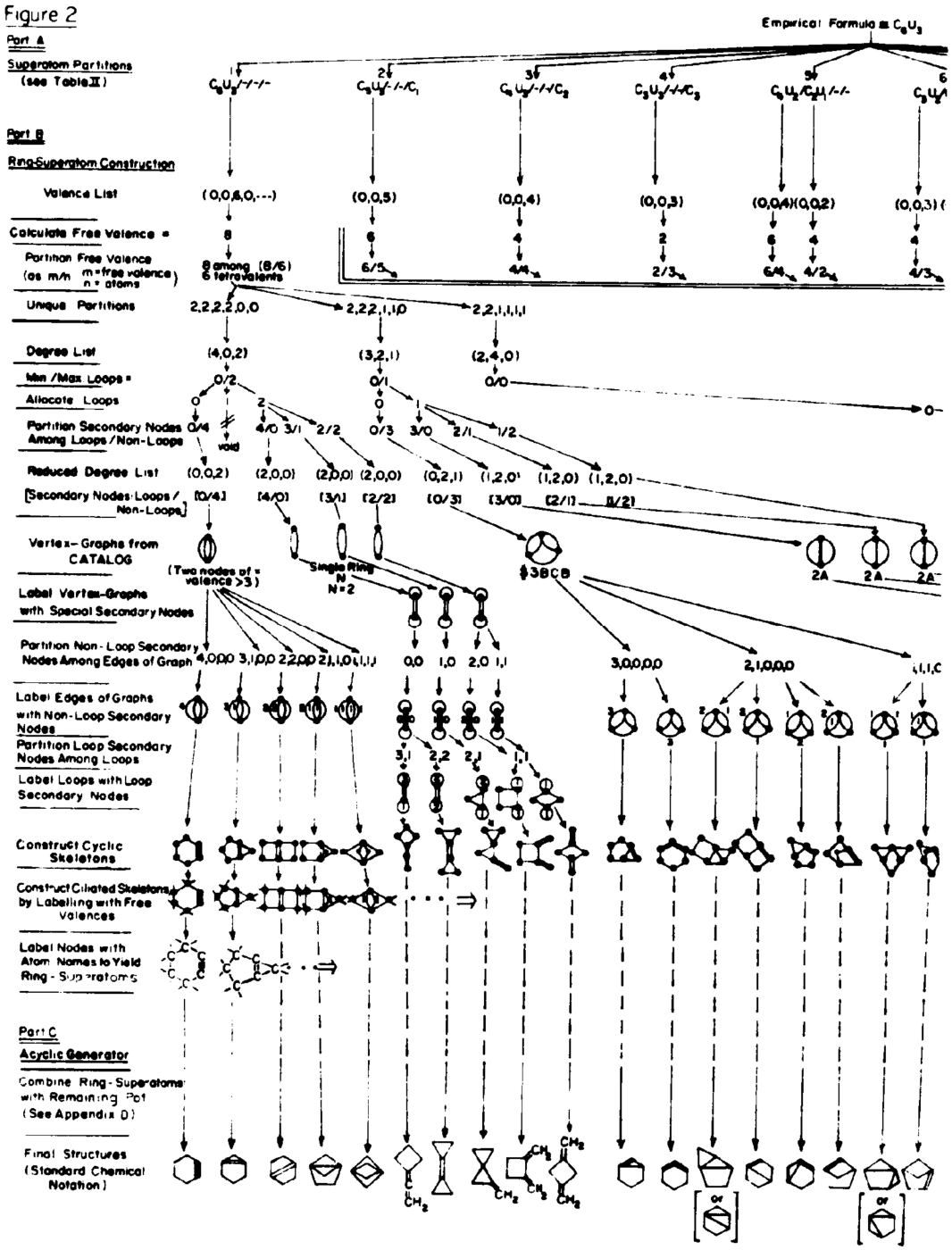
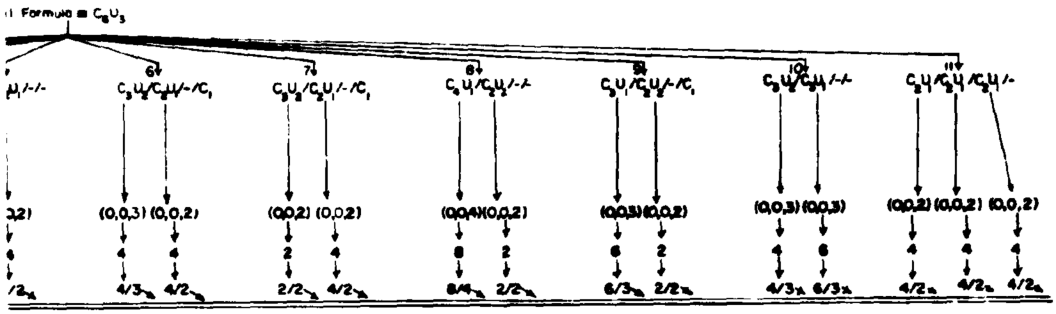

Empirical Formula
Part A: Form Superatom Partitions
Partition No.:
1
2
3 . . .
Consists of:
Superatompot
Remaining Pot
Superatompot
Remaining Pot
1
1
2
. . .
Part B: Construct Ring-superatoms
Ring-superatoms:
a, b, c, ...
j, k, l, . . .
p, q, r, . . .
Part C: Construct Structures
Combine Ring-superatoms with Remaining Pot
I, II, III, . . .
CI, CII, CIII, . . .

Figure 2


Empirical Formula ≡ C_8U_3
Part A
Superatom Partitions
(see Table II)
Part B
Ring-Superatom Construction
Valence List
Calculate Free Valence =
Partition Free Valence
(as m/n m = free valence n = atoms)
Unique Partitions
Degree List
Min /Max Loops =
Allocate Loops
Partition Secondary Nodes Among Loops / Non-Loops
Reduced Degree List
[Secondary Nodes: Loops / Non-Loops]
Vertex-Graphs from CATALOG
(Two nodes of = valence > 3)
Single Ring N N=2
Label Vertex-Graphs with Special Secondary Nodes
Partition Non-Loop Secondary Nodes Among Edges of Graph
Label Edges of Graphs with Non-Loop Secondary Nodes
Partition Loop Secondary Nodes Among Loops
Label Loops with Loop Secondary Nodes
Construct Cyclic Skeletons
Construct Ciliated Skeletons by Labelling with Free Valences
Label Nodes with Atom Names to Yield Ring - Superatoms
Part C
Acyclic Generator
Combine Ring - Superatoms with Remaining Pot (See Appendix D)
Final Structures (Standard Chemical Notation)
void
2A
3BCB



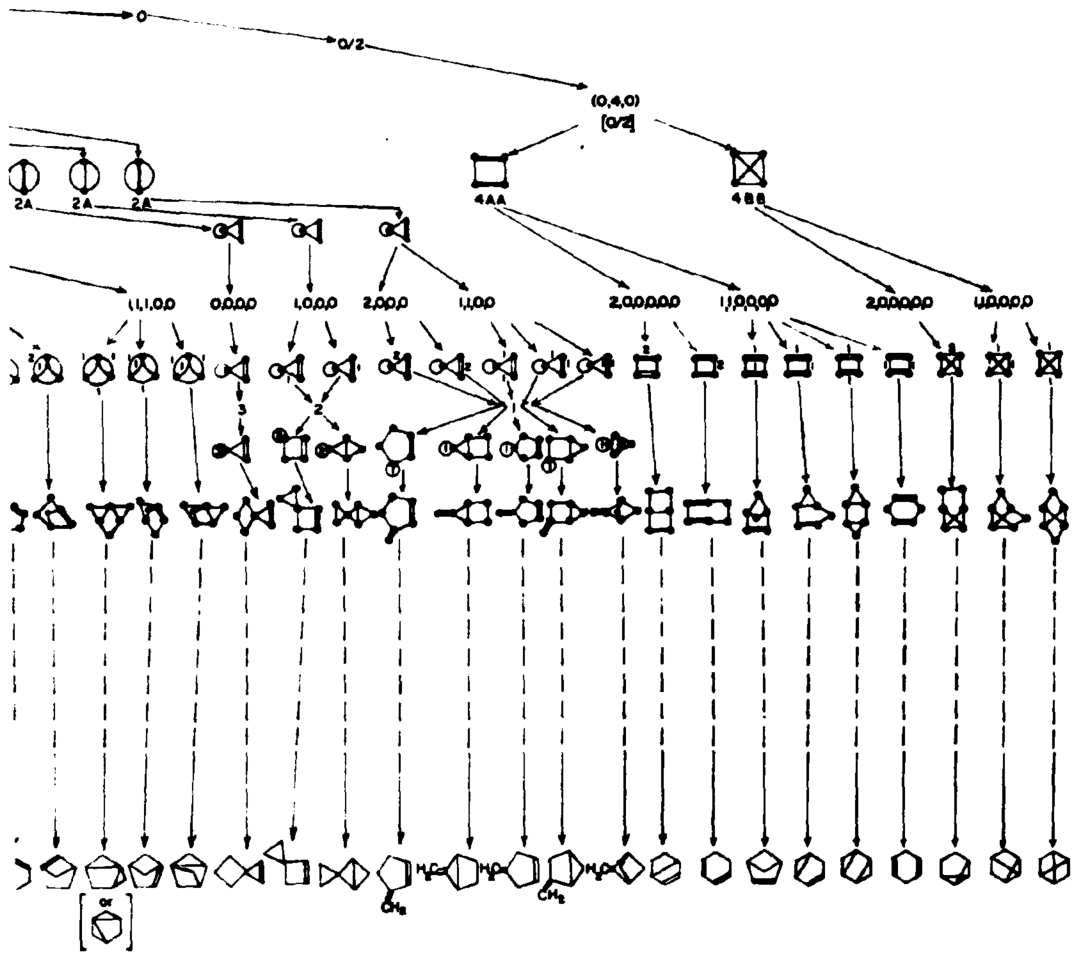


Figure 3

Category A. **BOND CENTROID**

List of Superatoms [$-C\equiv C-$, $>C=C<$, C , C]

Partition into 2 parts

$-C\equiv C-$, $>C=C< / C_2$ | $-C\equiv C-$, C / $>C=C<$, C

Part Number	1a	1b	2a	2b
Generate Radicals for each part [See Table VIII]	3 radicals	1 radical	2 radicals	3 radicals

Combine Radicals in pairs to form Molecules

(3 × 1 =) 3 molecules

$CH_3-CH_2-C\equiv C-CH=CH_2$

$CH_3-CH_2-CH=CH-C\equiv CH$

$CH_3-CH_2-C(=CH_2)-C\equiv CH$

(2×3=) 6 molecules

$CH_3-CH=CH-C\equiv C-CH_3$

$CH_3-CH=CH-CH_2-C\equiv CH$

$CH_3-C(=CH_2)-C\equiv C-CH_3$

$CH_3-C(=CH_2)-CH_2-C\equiv CH$

$CH_2=CH-CH_2-C\equiv C-CH_3$

$CH_2=CH-CH_2-CH_2-C\equiv CH$

Figure 4

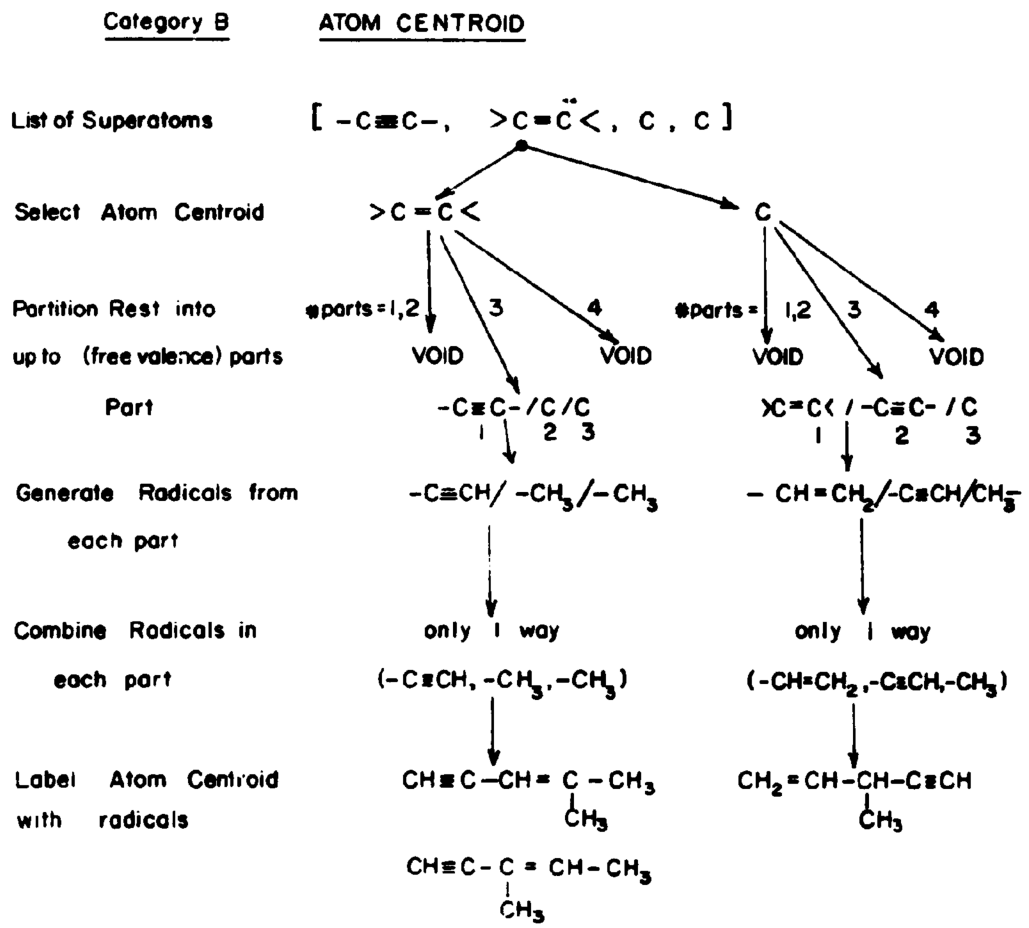

Category B
ATOM CENTROID
List of Superatoms
[-C≡C-, >C=C<, C, C]
Select Atom Centroid
>C=C<
C
Partition Rest into up to (free valence) parts
#parts = 1,2
3
4
VOID
VOID
#parts = 1,2
3
4
VOID
VOID
Part
-C≡C-/C/C
1 2 3
>C=C< / -C≡C- / C
1 2 3
Generate Radicals from each part
-C≡CH/ -CH3/-CH3
- CH=CH2/-C≡CH/CH3-
Combine Radicals in each part
only 1 way
(-C≡CH, -CH3, -CH3)
only 1 way
(-CH=CH2, -C≡CH, -CH3)
Label Atom Centroid with radicals
CH≡C-CH= C -CH3
CH3
CH≡C- C = CH-CH3
CH3
CH2=CH-CH-C≡CH
CH3

Figure 5

GENERATION OF RADICALS