Molecules in Silico: A Graph Description of Chemical Reactions†

Adalbert Kerber,*,‡ Reinhard Laue,‡ Markus Meringer,§ and Christoph Rücker||

Department of Mathematics, University of Bayreuth, 95440 Bayreuth, Germany, Kiadis BV, Zernikepark 6-8, 9747 AN Groningen, The Netherlands, and Biocenter, University of Basel, Klingelbergstrasse 70, 4056 Basel, Switzerland

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A general mathematical description, mostly in terms of graph theory, is given for reactions of organic chemistry. The corresponding computer program generates all products that can result from a given set of starting materials interacting according to a given set of reaction schemes. Example reactions from combinatorial chemistry, synthetic organic chemistry, and mass spectroscopic structure elucidation are considered in detail.

1. INTRODUCTION

Mostly building on the Dugundji−Ugi theory,[1] several authors devised systems for representing organic reactions in silico, focusing on various purposes. Databases for reaction retrieval such as Beilstein Crossfire contain reactions that are pairs of specific starting materials and specific products. Synthesis planning programs working in the retrosynthetic direction are well-known.[2] An early program generated intermediates to link given starting materials and products.[3] Of more recent origin are programs that use kinetic information, obtained directly from experiments,[4] via a quantitative structure−property relationship (QSPR) approach,[5] or from quantum−chemical calculations,[6] for the semiquantitative prediction of reaction mixtures. There are attempts to classify known general reactions and even to predict novel reaction types.[7]

The aim of our approach is to generate, from a given set of starting materials and a given set of general reactions, all possible products, including those derived from intermediates interacting according to the prescribed reactions. The purpose of the present paper is to detail the mathematical concepts that underlie our reaction module incorporated in MOLGEN-COMB[8] and MOLGEN-QSPR.[9−12]

2. MOLECULAR GRAPHS

The graph model for a description of chemical reactions, following the approach of Fujita[13] and Temkin et al.,[14] is based on our formulation of molecular graphs.[15,16] These are multigraphs consisting of vertices representing atoms and edges representing covalent bonds. The bonds may be single, double, or triple bonds. The vertices are colored by the symbols of chemical elements and of atomic states defined as follows.

2.1. Definition (Atomic State). An atomic state is a quadruple[17]

$$S := (v_s, p_s, q_s, r_s)$$

where the positive integer v_s identifies the valence, that is, the number of covalent bonds in which the atom is involved, with a double and triple bond contributing two and three, respectively; the non-negative integer p_s indicates the number of free electron pairs (lone pairs); the integer q_s denotes the charge associated with the atom, while $r_s \in \mathbb{B} := \{true = 1, false = 0\}$ shows whether or not the atom bears an unpaired electron. Such a state is called a ground state if $q_s = 0$ and $r_s = false$.

For each chemical element *X*, we introduce the set $\mathcal{Z}_X$ of admissible atomic states. Its definition clearly depends on the particular chemistry under investigation. For example, the default atomic state for carbon is (4, 0, 0, 0), which allows to construct most nonionic organic compounds that are not free radicals. If one is interested in carbocations, carbanions, or free radicals, the corresponding atomic states should be admitted, for example, (3, 0, 1, 0), (3, 1, −1, 0), and (3, 0, 0, 1), respectively. If one is interested in carbenes or isonitriles, for example, in the context of Ugi multicomponent reactions, the atomic state (2, 1, 0, 0) should be allowed. Note that a particular atomic state may include various bond patterns. Thus, (4, 0, 0, 0) is the state of a neutral carbon atom involved in four single bonds, or in one double and two single bonds, or in two double bonds, or in a single and a triple bond, that is, any saturated, olefinic, aromatic, central allenic, or acetylenic carbon atom, or a carbon in a functional group including carbonyl or nitrile.

The elements are gathered in sets $\mathcal{E}$ such as

$$\mathcal{E}_4 := \{\mathrm{H, C, N, O}\}$$

or its extension

$$\mathcal{E}_{11} := \{\mathrm{H, C, N, O, F, Si, P, S, Cl, Br, I}\}$$

2.2 Definition (Molecular Graph). Let $\mathcal{E}$ denote a set of chemical elements, and assume that $\mathcal{Z}_\mathcal{E}$ indicates the set of

† Dedicated to Professor Nenad Trinajstić on the occasion of his 70th birthday.

* Corresponding author phone: +49 921 553387; fax: +49 921 553385; e-mail: kerber@uni-bayreuth.de.

‡ University of Bayreuth.

§ Kiadis BV.

|| University of Basel.

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all the admissible atomic states of the elements in $\mathcal{E}$. In formal mathematical terms

$$\mathcal{Z}_\varepsilon := \bigcup_{X \in \mathcal{E}} \mathcal{Z}_X$$

A molecular graph describing a molecule of n atoms, numbered from 0 to $n-1$ and taken from $\mathcal{E}$, is a triple

$$(\varepsilon, \zeta, \gamma)$$

where ε is a sequence of length n, consisting of element symbols, that is[18]

$$\varepsilon = (\varepsilon(0), ..., \varepsilon(n-1)) \in \mathcal{E}^n$$

The second component ζ is a sequence $\zeta = (\zeta(0), ..., \zeta(n-1))$ of n atomic states, where the ith component is an admissible state of atom i

$$\zeta(i) \in \mathcal{Z}_{\varepsilon(i)} \tag{1}$$

The third component γ is a connected multigraph consisting of n vertices and edges that are at most 3-fold, that is, elements of the set $4 = \{0, 1, 2, 3\}$, for short,[19]

$$\gamma \in \mathcal{G}^c_{n,4}$$

Its vertices are numbered from 0 to $n-1$ and colored by the element symbols $\varepsilon(i)$, the components of ε. The degree of the ith vertex of the graph is equal to the valence of atom i

$$\deg(i) = v_{\zeta(i)} \tag{2}$$

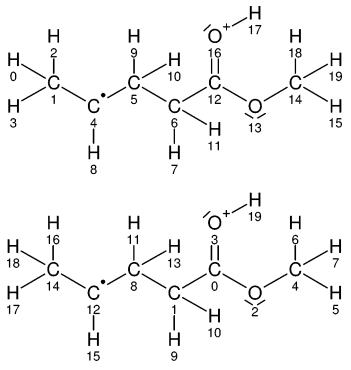
By $\mathcal{M}^c_n$ we denote the set of connected molecular graphs on n atoms, by $\mathcal{M}^c$ the set of all connected molecular graphs.

Summarizing, we can abbreviate our main definition as follows: A molecular graph, modeling a molecule consisting of n atoms taken from the set of elements $\mathcal{E}$, and with their states in $\mathcal{Z}_\mathcal{E}$, is a triple

$$(\varepsilon, \zeta, \gamma) \in (\mathcal{E}^n \times \mathcal{Z}^n_\mathcal{E} \times \mathcal{G}^c_{n,4})$$

that fulfills eqs 1 and 2.

Here is an example of two molecular graphs modeling an ion radical obtained from methyl pentanoate:



In such a drawing, pecularities of atomic states are represented by several symbols, a plus (+) for a single positive charge, a bar (−) for a free electron pair, and a dot (·) for an unpaired electron.

Two such molecular graphs $(\varepsilon, \zeta, \gamma)$ and $(\varepsilon', \zeta', \gamma')$ describe the same structure if and only if they are the same up to renumbering, which means that there is a permutation π such that

$$(\varepsilon, \zeta, \gamma)^\pi = (\varepsilon', \zeta', \gamma')$$

where

$$(\varepsilon, \zeta, \gamma)^\pi = (\varepsilon^\pi, \zeta^\pi, \gamma^\pi)$$

defined by[20]

$$\varepsilon^\pi(i) = \varepsilon(\pi(i)),$$
$$\zeta^\pi(i) = \zeta(\pi(i)),$$
$$\gamma^\pi(\{i, j\}) = \gamma(\{\pi(i), \pi(j)\})$$

In mathematical terms, we are faced with the following action of the symmetric group S_n:

$$(\mathcal{E}^n \times \mathcal{Z}^n_\mathcal{E} \times \mathcal{G}^c_{n,4}) \times S_n \rightarrow \mathcal{E}^n \times \mathcal{Z}^n_\mathcal{E} \times \mathcal{G}^c_{n,4}$$

$$((\varepsilon, \zeta, \gamma), \pi) \mapsto (\varepsilon, \zeta, \gamma)^\pi$$

This action, as every action of a group on a set, induces an equivalence relation, the classes of which are called orbits. For example,

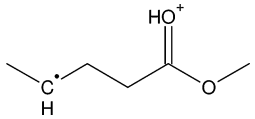
$$S_n((\varepsilon, \zeta, \gamma)) = \{(\varepsilon, \zeta, \gamma)^\pi \mid \pi \in S_n\}$$

is the orbit of the molecular graph $(\varepsilon, \zeta, \gamma)$. The conditions 1 and 2 in the definition of molecular graphs are preserved by this operation. Hence, a structural formula of a molecule with n atoms from $\mathcal{E}$ corresponds to an orbit of S_n on the set $(\mathcal{E}^n \times \mathcal{Z}^n_\mathcal{E} \times \mathcal{G}^c_{n,4})$; that is, the set of structural formulas of molecules built from n atoms in $\mathcal{E}$ is the set of orbits of the symmetric group

$$S_n // \mathcal{M}^c_n = \{S_n((\varepsilon, \zeta, \gamma)) \mid (\varepsilon, \zeta, \gamma) \in \mathcal{M}^c_n\}$$

Hence, the problem of constructing all structural formulas, that is, the structural isomers corresponding to a certain molecular formula, amounts to finding a complete system of representatives of these orbits of the symmetric group. MOLGEN is a software package that solves this problem efficiently.[21,22]

The two molecular graphs shown above of course belong to the same orbit. A representative of this orbit can be drawn as follows:



where for the sake of simplicity we erased the atom numbering, the symbols for free electron pairs, hydrogen atoms adjacent to carbon atoms in their ground state, and the symbols of such carbon atoms.

3. MOLECULAR SUBSTRUCTURES

It is an old experience in organic chemistry that a reaction takes place at a specific position rather than anywhere in a molecule. Such reactive sites are, for example, the classical functional groups, or other particular structural elements

called substructures. For this reason, in the following, a precise definition of the term substructure for multigraphs is given.

3.1. Definition (Subgraph). Let $\gamma \in \mathscr{G}_{n,m}$ be a multigraph on the set n of vertices, the edge multiplicities less than m, and $V \subseteq n$ a nonempty subset of n. $\gamma' \in \mathscr{G}_{V,m}$ is an ordinary subgraph of γ, if

$$\forall\, e \in E_{\gamma'} :\ \gamma'(e) \le \gamma(e)$$

where $E_{\gamma'}$ denotes the set of edges of γ'. We write $\gamma' \subseteq \gamma$ to indicate this. If the stronger condition

$$\forall\, e \in E_{\gamma'} :\ \gamma'(e) = \gamma(e)$$

holds, γ' is called a multiplicity-preserving subgraph of γ ($\gamma' \subseteq^m \gamma$). If finally

$$\forall\, e \in \binom{V}{2} :\ \gamma'(e) = \gamma(e)$$

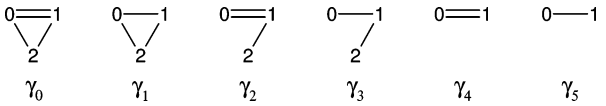
we call γ' an induced subgraph of γ ($\gamma' \subseteq^i \gamma$).

Note that with the above definitions the following implications hold:

$$\gamma' \subseteq^i \gamma \Rightarrow \gamma' \subseteq^m \gamma \quad \text{and} \quad \gamma' \subseteq^m \gamma \Rightarrow \gamma' \subseteq \gamma$$

that is, an induced subgraph is a multiplicity-preserving subgraph, as well, and a multiplicity-preserving subgraph is, of course, an ordinary subgraph.

3.2. Example. We illustratively examine the following multigraphs for subgraph relations to γ_0:



We have $\gamma_1 \subseteq \gamma_0$, but γ_1 is not a multiplicity-preserving subgraph of γ_0; $\gamma_2 \subseteq^m \gamma_0$, but γ_2 is not an induced subgraph of γ_0; $\gamma_3 \subseteq \gamma_0$, but γ_3 is not a multiplicity-preserving subgraph of γ_0; $\gamma_4 \subseteq^i \gamma_0$; $\gamma_5 \subseteq \gamma_0$, but γ_5 is not a multiplicity-preserving subgraph of γ_0.

To appreciate the difference between a multiplicity-preserving and an induced subgraph, consider γ_3 and γ_1: $\gamma_3 \subseteq^m \gamma_1$, because for all edges in γ_3 the multiplicities are equal to the multiplicities of the corresponding edges in γ_1. However, there is a pair of vertices in γ_3, the nonedge $e = \{0, 2\}$, with $\gamma_3(e) \neq \gamma_1(e)$.

For $\gamma \in \mathscr{G}_{n,m}$ and $\varnothing \neq V \subseteq n$, the induced subgraph $\gamma' \in \mathscr{G}_{V,m}$ of γ is uniquely determined. Therefore, we call γ' the induced subgraph of γ on V, and we write $\gamma' = \gamma|_V$. The set of induced subgraphs $\gamma|_{V_0}$, ..., $\gamma|_{V_{k-1}}$ on the connectivity components V_0, ..., V_{k-1} of γ is denoted by $\mathrm{Con}(\gamma)$.

3.3. Definition (Embedding). Let $\gamma \in \mathscr{G}_{n,m}$, $V \subseteq n$ be a nonempty subset of n, and $\gamma' \in \mathscr{G}_{V,m}$. Let, furthermore, n^V_{inj} denote the set of injective mappings from V to n. Such a mapping ϕ is called an embedding of γ' in γ

- as an ordinary subgraph, if

$$\forall\, \{i, j\} \in E_{\gamma'} :\ \gamma'(\{i, j\}) \le \gamma(\{\phi(i), \phi(j)\})$$

- as a multiplicity-preserving subgraph, if

$$\forall\, \{i, j\} \in E_{\gamma'} :\ \gamma'(\{i, j\}) = \gamma(\{\phi(i), \phi(j)\})$$

- as an induced subgraph, if

$$\forall\, \{i, j\} \in \binom{V}{2} :\ \gamma'(\{i, j\}) = \gamma(\{\phi(i), \phi(j)\})$$

We write $\gamma' \subseteq_\phi \gamma$, $\gamma' \subseteq^m_\phi \gamma$, or $\gamma' \subseteq^i_\phi \gamma$, respectively. Furthermore, sets of embeddings are denoted as follows:

$$\mathrm{Emb}_{\subseteq}(\gamma', \gamma) := \{\phi \in n^V_{\mathrm{inj}} \mid \gamma' \subseteq_\phi \gamma\}$$

$$\mathrm{Emb}_{\subseteq^m}(\gamma', \gamma) := \{\phi \in n^V_{\mathrm{inj}} \mid \gamma' \subseteq^m_\phi \gamma\}$$

$$\mathrm{Emb}_{\subseteq^i}(\gamma', \gamma) := \{\phi \in n^V_{\mathrm{inj}} \mid \gamma' \subseteq^i_\phi \gamma\}$$

In order to apply the concept of subgraphs to molecular graphs, we define the molecular substructure.

3.4. Definition (Substructure). Let $M = (\varepsilon, \zeta, \gamma) \in \mathscr{M}_n$ be a molecular graph and $k \le n$. A triple

$$S = (\varepsilon', \zeta', \gamma') \in \mathscr{E}^k \times \mathscr{Z}^k_{\mathscr{E}} \times \mathscr{G}_{k,4} =: \mathscr{S}_k$$

is

- an ordinary substructure of M, if

$$\exists\, \phi \in \mathrm{Emb}_{\subseteq}(\gamma', \gamma) :\ \forall\, i \in k :\ \varepsilon(\phi(i)) = \varepsilon'(i) \text{ and } \zeta(\phi(i)) = \zeta'(i)$$

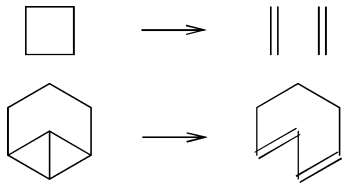
- a multiplicity-preserving substructure of M, if

$$\exists\, \phi \in \mathrm{Emb}_{\subseteq^m}(\gamma', \gamma) :\ \forall\, i \in k :\ \varepsilon(\phi(i)) = \varepsilon'(i) \text{ and } \zeta(\phi(i)) = \zeta'(i)$$

- an induced substructure of M, if

$$\exists\, \phi \in \mathrm{Emb}_{\subseteq^i}(\gamma', \gamma) :\ \forall\, i \in k :\ \varepsilon(\phi(i)) = \varepsilon'(i) \text{ and } \zeta(\phi(i)) = \zeta'(i)$$

A chemist looking for a substructure usually is interested in what we call a multiplicity-preserving substructure, rather than what we call an ordinary substructure or an induced substructure. Thus, ethane is not usually considered a substructure of ethene, at least in the context of possible reactions. On the other hand, cyclobutane is considered a substructure of tricyclo[4.1.0.0^{2,7}]heptane, with the cyclobutane graph being a multiplicity-preserving, not an induced, subgraph in the tricyclo[4.1.0.0^{2,7}]heptane molecular graph.[23] This is demonstrated in the following specific reactions, both being considered possible:



In order to allow a more flexible description of structural properties, in our computer programs, further concepts are integrated:

- In molecular substructures, alternatives for chemical elements, atomic states, and bond multiplicities are allowed. In this case, we speak of ambiguous molecular substructures.
- Substructure restrictions are introduced in order to describe graph-theoretical properties such as distances be-

tween atoms, bond patterns, and neighborhoods of atoms, or prescribed and forbidden ring sizes.

For detailed descriptions of ambiguous molecular substructures and substructure restrictions, see refs 16 and 24.

4. CHEMICAL REACTIONS

To every chemist, it is obvious that a specific reaction is characterized by its reactant(s) and its product(s). At the same time, the essential aspect of a reaction is what happens to the starting material(s), so that a reaction may be described by detailing its reactant(s) and the changes that occur. Whenever corresponding changes occur to different reactants, such reactions belong to the same class. In the following, these ideas are expressed in mathematical terms. The basic definition is as follows.

4.1. Definition (Chemical Reaction). Assume a positive integer n and a set $\mathcal{E}$ of chemical elements together with $\mathcal{Z}_{\mathcal{E}} = \cup_{X \in \mathcal{E}} \mathcal{Z}_X$, the set of admissible atomic states of the elements in $\mathcal{E}$. An ordered pair

$$C := (M, M') \in \mathcal{M}_n \times \mathcal{M}_n$$

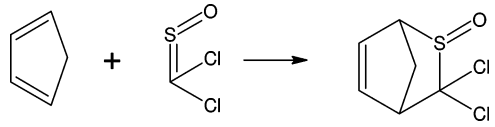
consisting of two molecular graphs $M = (\varepsilon, \zeta, \gamma)$ and $M' = (\varepsilon', \zeta', \gamma')$ is called a chemical reaction if $\varepsilon = \varepsilon'$. M is the reactant graph and M' the graph of the product. The set Con(M) of connectivity components of M is the set of starting materials, the set Con(M') of connectivity components of M' the set of products. By $\mathcal{C}_n$, we shall indicate in the following the set of chemical reactions with n atoms involved.

Instead of the mathematical pair notation (M, M'), chemists use the mapping notation, writing

$$M \rightarrow M'$$

Chemists usually link the components of the reactant or product graph by + signs.

4.2. Example. The following figure shows the Diels–Alder reaction of cyclopentadiene and thiophosgene *S*-oxide.[25] The reactant graph (left) and the product graph (right) consist of two components and a single component, respectively:



It is obvious that the changes of atomic states and bonds caused by chemical reactions are of particular interest. Concepts similar to the following were earlier introduced by Dugundji and Ugi,[1] Fujita,[13] and Temkin et al.[14]

4.3. Definition (Reaction Graph of Changes, Bond Change Graph). The reaction graph of changes is defined to be the pair

$$\Delta C := (\Delta\zeta, \Delta\gamma) \in \Delta\mathcal{Z}^n \times \mathcal{G}_{n,[-3,3]} =: \Delta\mathcal{C}_n$$

the components $\Delta\zeta$ and $\Delta\gamma$ of which are defined as follows:

(i) $\Delta\zeta$ is a sequence

$$(\Delta\zeta(0), ..., \Delta\zeta(n-1))$$

the ith component of which is

$$\Delta\zeta(i) := (\Delta v_i, \Delta p_i, \Delta q_i, \Delta r_i) \in \mathbb{Z} \times \mathbb{Z} \times \mathbb{Z} \times \mathbb{B} =: \Delta\mathcal{Z}$$

describing the change of the state of atom i: $\Delta v_i := v_{\zeta'(i)} - v_{\zeta(i)}$ means the change of valence of atom i, $\Delta p_i := p_{\zeta'(i)} - p_{\zeta(i)}$ denotes the change of the number of free electron pairs of atom i, $\Delta q_i := q_{\zeta'(i)} - q_{\zeta(i)}$ is the change of charge on atom i, while $\Delta r_i := r_{\zeta'(i)} \dot{\vee} r_{\zeta(i)}$ indicates the change of the radical character at atom i.[26]

For short, $\Delta\zeta$ is the distribution of the changes of atomic states caused by reaction C.

(ii) The second component of the reaction graph of changes is the graph $\Delta\gamma$, whose vertices are the atoms 0, ..., $n-1$, and atom i is connected to atom j if and only if the bond between these atoms is changed during the reaction. That is, vertex i is connected to vertex j if and only if $\gamma'(\{i,j\}) - \gamma(\{i,j\}) \neq 0$. Moreover, this edge is labeled by the difference

$$\Delta\gamma(\{i,j\}) := \gamma'(\{i,j\}) - \gamma(\{i,j\})$$

Since the bond multiplicities in γ and in γ' are at most 3, we obtain

$$\Delta\gamma(\{i,j\}) \in [-3, 3]$$

for short:

$$\Delta\gamma \in \mathcal{G}_{n,[-3,3]}$$

This label $\Delta\gamma(\{i,j\})$ describes the change of bond multiplicity between atoms i and j. $\Delta\gamma$ is therefore called the bond change graph of C.

We are now able to formulate an important definition of the present paper, a mathematical model for reactions in organic chemistry on the level of integral chemistry.[1]

4.4. Definition (Reaction Graph). A chemical reaction C is completely described by its reactant graph M together with ΔC. Therefore, we call the quintuple

$$(\varepsilon, \zeta, \gamma, \Delta\zeta, \Delta\gamma)$$

the reaction graph of C.

Using the above notation of a chemical reaction, we write

$$M' = \Delta C \circ M$$

where ΔC is applied to M in the following way:

$$\Delta C \circ M = (\Delta\zeta, \Delta\gamma) \circ (\varepsilon, \zeta, \gamma) := (\varepsilon, \Delta\zeta \circ \zeta, \Delta\gamma \circ \gamma)$$

and for $i, j \in n$, $i \neq j$,

$$(\Delta\zeta \circ \zeta)(i) := \Delta\zeta(i) \circ \zeta(i)$$

$$(\Delta\gamma \circ \gamma)(\{i,j\}) := \gamma(\{i,j\}) + \Delta\gamma(\{i,j\})$$

The distribution of atomic states in the product is

$$\Delta\zeta(i) \circ \zeta(i) := (v_{\zeta(i)} + \Delta v_i, p_{\zeta(i)} + \Delta p_i, q_{\zeta(i)} + \Delta q_i, r_{\zeta(i)} \dot{\vee} \Delta r_i)$$

4.5. Definition (Reaction Center). Assume a chemical reaction

$$C = ((\varepsilon, \zeta, \gamma), (\varepsilon, \zeta', \gamma')) \in \mathcal{C}_n$$

Then

$$\mathrm{Cen}(C) := \{0 \le i \le n-1 \mid \zeta(i) \neq \zeta'(i) \vee \exists j:\ \gamma(\{i,j\}) \neq \gamma'(\{i,j\})\}$$

is called the reaction center of C.

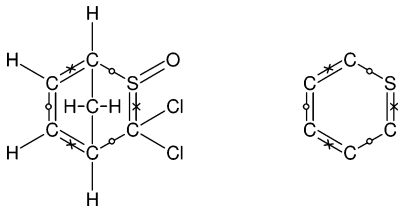
Hence, by definition, a reaction center consists of those atoms whose atomic states or bonds are changed in the reaction. Thus, the reaction may alternatively be described by its reactant graph, the reaction center, and the changes of states and bonds.

4.6. Definition (Reaction Center Graph). Let C denote a chemical reaction. The subgraph induced by the reaction center

$$\mathrm{RCG}(C) := (\varepsilon|_{\mathrm{Cen}(C)}, \zeta|_{\mathrm{Cen}(C)}, \gamma|_{\mathrm{Cen}(C)}, \Delta\zeta|_{\mathrm{Cen}(C)}, \Delta\gamma|_{\mathrm{Cen}(C)})$$

is called the reaction center graph of C.

4.7. Example. The following picture shows the reaction graph (left) and the reaction center graph (right) of the above Diels−Alder reaction:



Bonds that are formed in the reaction are indicated by small circles '∘'; bonds that are broken are indicated by crosses '×'. Thus, for the sake of simplicity, these symbols replace bond labels +1 and −1.

Finally, the reaction center graph can be split into the reaction substructure (left) and the bond change graph (right):

It is often observed that two nonidentical reactions are essentially the same. In such cases, the reaction center graphs are identical or similar. Compare the above reaction with the analogous reaction between 1,3-butadiene and thiophosgene *S*-oxide, or the reactions of cyclopentadiene or 1,3-butadiene with the dibromo analog of thiophosgene *S*-oxide: all the reaction center graphs are identical. In the cycloaddition of a 1,3-diene and maleic acid anhydride, the reaction center graph is as before except that the S is replaced by a C, and this reaction center graph obviously describes the essence of the Diels−Alder class of reactions.

4.8. Definition (Reaction Scheme). Assume a natural number k. A reaction scheme is a triple

$$R := (S, \Delta\zeta, \Delta\gamma) \in \mathcal{S}_k \times \Delta\mathcal{Z}^k \times \mathcal{G}_{k,[-3,3]} =: \mathcal{R}_k$$

consisting of a substructure S, the distribution of the change of states $\Delta\zeta$, and the bond change graph $\Delta\gamma$. In this context, S is also called the reaction substructure.

This definition allows to describe one-reactant reactions such as cleavages and rearrangements as well as synthesis reactions with arbitrary numbers of reactants. Example 4.7 shows a canonical way to obtain a suitable reaction substructure from a specific reaction. However, the reaction substructure may be defined in a more or less restrictive manner in order to allow fewer or more reaction products to result from application of the reaction scheme, respectively.

The application of a reaction scheme $R = (S, \Delta\zeta, \Delta\gamma) \in \mathcal{R}_k$ to a molecular graph $M = (\varepsilon, \zeta, \gamma) \in \mathcal{M}_n$ is done in two steps. First, we search for an embedding of the reaction substructure S in M. If we find such an embedding $\phi \in \mathrm{Emb}_{\subseteq^m}(S, M)$, then we apply both the distribution of change of states and the bond change graph to M in the following way: ϕ induces the mapping

$$-^{\phi}:\ \Delta\mathcal{C}_k \to \Delta\mathcal{C}_n,\quad (\Delta\zeta, \Delta\gamma) \mapsto (\Delta\zeta, \Delta\gamma)^{\phi} := (\Delta\zeta^{\phi}, \Delta\gamma^{\phi})$$

where, for all $i \in n$,

$$\Delta\zeta^{\phi} := \begin{cases} \Delta\zeta(\phi^{-1}(i)) & \text{if } i \in \phi(k) \\ (0,0,0,\mathit{false}) & \text{else} \end{cases}$$

and, for $i, j \in n$, $i \neq j$,

$$\Delta\gamma^{\phi} := \begin{cases} \Delta\gamma(\{\phi^{-1}(i), \phi^{-1}(j)\}) & \text{if } i,j \in \phi(k) \\ 0 & \text{else} \end{cases}$$

An application of R to M with respect to ϕ can be defined as

$$R \circ_{\phi} M := (\Delta\zeta, \Delta\gamma) \circ_{\phi} M := (\Delta\zeta, \Delta\gamma)^{\phi} \circ M$$

Note, however, that $R \circ_{\phi} M$ does not necessarily fulfill requirements 1 and 2 of definition 2.2 (molecular graph).

4.9. Definition (Set of Product Graphs). Assume positive natural numbers k and n, where $k \le n$, $R = (S, \Delta\zeta, \Delta\gamma) \in \mathcal{R}_k$ is a reaction scheme, and $M \in \mathcal{M}_n$ is a molecular graph. The set of product graphs obtained by application of R to M is

$$\mathrm{Prod}_R(M) := \{R \circ_{\phi} M \in \mathcal{M}_n \mid \phi \in \mathrm{Emb}_{\subseteq^m}(S, M)\}$$

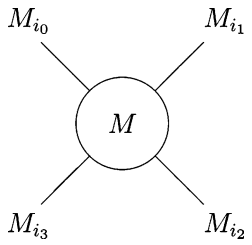
This mathematical model allows simulation of chemical reactions, in the sense of generating all products that may arise from a given set of reactants and a given reaction scheme.

Quite a different question is that for the quantitative result of chemical reactions, that is, for the amounts (concentrations) of products in the case of competing reactions. The outcome depends on reactivities, that is, on free enthalpies of activation of the competing reactions and on temperature, and thus does not seem amenable to graph theoretic modeling, at least at present.

5. LIBRARIES OBTAINED FROM A CENTRAL MOLECULE

Assume a central molecule M and reaction partners M_i, $i \in a$, together with a reaction scheme $R = (S, \Delta\zeta, \Delta\gamma)$. We suppose that R means a two-component synthesis; that is, the graph underlying S consists of two connectivity components A and B. We assume that A is embedded in M by k nonoverlapping ϕ_j, $j \in k$. For each j, the atoms defined in M by ϕ_j are a reactive site. Each reaction partner M_i, on the other hand, is assumed to contain a single embedding of B, the other component of the reaction substructure.

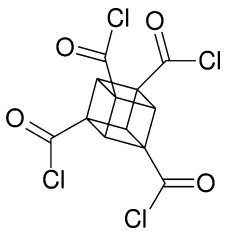
By applying the reaction scheme, we attach the reaction partners in various combinations to the reactive sites of the central molecule. For $k = 4$, we may sketch the situation as follows:



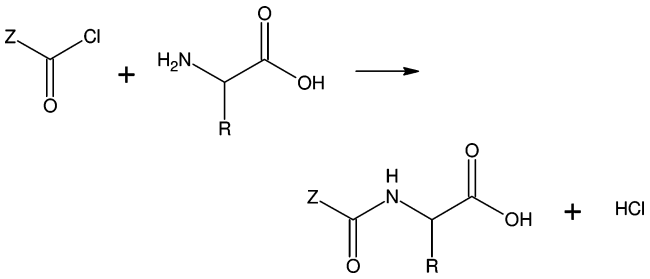
Here, the index $i_j \in a$ in the substituent symbols M_{i_j} refers to the identity of the substituent; the subindex $j \in k$ refers to the numbering of the reactive sites in the central molecule M.

The essentially different attachments of substituents to the central molecule can be generated using the symmetry group of M.[27] The automorphism group Aut(M) acts on the reactive sites of M and induces a subgroup G of the symmetric group S_k acting on these sites. The essentially different attachments are the orbits of the symmetry group G on the set of all the a^k attachments.

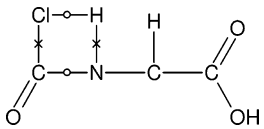
5.1. Example. As an example, we consider the exhaustive amidation of a particular cubanetetracarboxylic acid tetrachloride as a central molecule:[28,29]



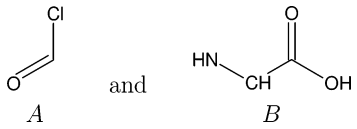
$a = 20$ natural amino acids are attached to this central molecule as shown below. An acyl chloride group reacts with an amino group in the α position to the carboxyl group:



Proline contains only one hydrogen bound to the N atom. To include proline, we define the reaction scheme in the following way:



The two connectivity components of the reaction substructure are



There are $k = 4$ embeddings of A found in the cubanetetracarboxylic acid tetrachloride, while there exists exactly one embedding of B in each of the 20 amino acids. Altogether, there are $20^4 = 160\,000$ possible attachments of four amino acid molecules to the central molecule. But with respect to the central molecule's automorphism group, the essentially different attachments are obtained as different orbits of the operation of the symmetric group S_4 applied to the set of 20^4 mappings. The result is a combinatorial library of 8855 different structures:

$$|20^4 // S_4| = 8855$$

This example shows the importance of a canonizer in the generation process.[30] Without it, using the combinatorial approach, we would need to carry out $\binom{160\,000}{2}$ isomorphism tests in order to get rid of the duplicates.

6. CONSTRUCTION OF REACTION NETWORKS

In the following, we describe how compound libraries are generated by the successive application of reaction schemes. Such libraries are of particular importance in structure elucidation, as well as in combinatorial chemistry.

Most chemical processes can be described as chemical reaction networks. Such a network is a bipartite directed graph. Its vertex set is partitioned into compounds and reactions; that is, the vertices represent either molecular graphs or reaction schemes. Its edges are directed, from reactants to their reactions, and from reactions to their products. While the same reaction scheme may occur in a chemical reaction network several times, a molecular graph can occur at most once, with its vertices (atoms) canonically labeled.

We shall generate for a given set of reactants and a given set of reaction schemes all molecular graphs that can occur. We shall run through a (partial) reaction network using a breadth-first strategy.

Initially, we have to generalize a few notions. Above, we introduced the application of a reaction scheme $R = (S, \Delta\xi, \Delta\gamma)$ to a single molecular graph $M \in \mathscr{M}$ in order to obtain the set of product graphs:

$$\mathrm{Prod}_R(M) = \{R \circ_\phi M \in \mathscr{M}_n \mid \phi \in \mathrm{Emb}_{\subseteq m}(S, M)\}$$

We extend this definition to sets of molecular graphs and sets of reaction schemes, starting from a set

$$\mathscr{L} = \{M_i \mid i \in l\} \subseteq \mathscr{M}^c$$

of connected molecular graphs. In order to evaluate the set of all possible products arising by an application of R to $\mathscr{L}$, we have to examine the connectivity components of the reaction substructure S:

$$\mathrm{Con}(R) := \mathrm{Con}(S)$$

That is, $|\mathrm{Con}(R)|$ is the maximum number of starting

materials involved in a reaction of the present kind. For the Diels−Alder reaction, this number is two. In the particular example reaction above, there are in fact two starting materials, though in an intramolecular Diels−Alder reaction, there is but one. Thus, for the Diels−Alder and many other typical synthetic reactions, all combinations (with repetition) of two species in the set of starting materials have to be considered as potentially reactive. "With repetition" means that, for example, a combination of two reactants may be made of two copies of the same species.

For the set of combinations with repetition of n objects out of a set of m objects, we introduce the notation $m^n_{\leq}$. This set is a subset of the set of distributions of n out of m objects to n positions (of which there are m^n). The subset condition is that the positions occupied do not matter; that is, all those distributions are considered equivalent that lead to the same result after the objects are arranged in increasing order. (We assume that a natural order is defined for the objects, as, e.g., for the natural numbers, or some initial or canonical numbering for molecular graphs.) Thus, the combinations with repetition are equivalent to weakly monotonously increasing mappings from n to m:

$$m^n_{\leq} := \{f \in m^n \mid \forall\, i:\ f(i) \leq f(i+1)\}$$

Using this, we can introduce the product graphs arising from an application of R to the library $\mathscr{L}$ as

$$\mathrm{Prod}_R(\mathscr{L}) := \bigcup_{k \in |\mathrm{Con}(R)|} \bigcup_{f \in I^k_{\leq}} \mathrm{Prod}_R\left(\bigoplus_{i \in k} M_{f(i)}\right)$$

$\oplus_{i\in k} M_{f(i)}$ is built by putting $M_{f(0)}$, ..., $M_{f(k-1)}$ together into one big (disconnected) molecular graph.

For a set $\mathscr{R}$ of reaction schemes, we can define

$$\mathrm{Prod}_{\mathscr{R}}(\mathscr{L}) := \bigcup_{R \in \mathscr{R}} \mathrm{Prod}_R(\mathscr{L})$$

Finally, we have to decompose the product graphs into connectivity components and to eliminate duplicates that may occur. For this reason, we define, for an arbitrary set $\mathscr{L}$ of molecular graphs

$$\mathrm{Con}(\mathscr{L}) := \bigcup_{M \in \mathscr{L}} \mathrm{Con}(M)$$

and

$$\kappa(\mathscr{L}) := \{\kappa(M) \mid M \in \mathscr{L}\}$$

Here, $\kappa(M)$ denotes the canonical labeling of M. Earlier, we described an algorithm that computes a canonical labeling.[30]

We are now able to formulate an algorithm for the construction of the library of products that can arise by application of the set of reaction schemes $\mathscr{R}$ to a given set of molecular graphs $\mathscr{L}$.

6.1. Algorithm. *MolLib*($\mathscr{L}$, $\mathscr{R}$)

(1) $\mathscr{L}_0 \leftarrow \kappa(\mathscr{L})$, $k \leftarrow 0$

(2) **while** $\mathscr{L}_k \neq \varnothing$ **do**

(3) $\quad k \leftarrow k + 1$

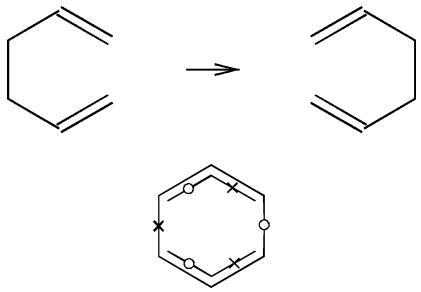
(4) $\quad \mathscr{L}_k \leftarrow \kappa\,(\mathrm{Con}(\mathrm{Prod}_{\mathscr{R}}\,(\bigcup_{i\in k} \mathscr{L}_i))) \backslash \bigcup_{i\in k} \mathscr{L}_i$

(5) $\quad$ *Output* ($\mathscr{L}_k$)

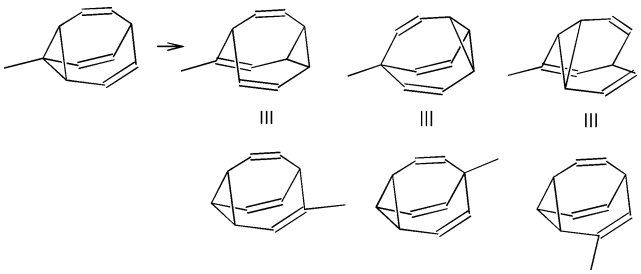
(6) **end**

This means that, in row 1, reactants are transformed into canonical forms, which after elimination of duplicates are assigned to $\mathscr{L}_0$. Of central importance is line 4. There, we construct from the already obtained libraries $\mathscr{L}_i$, $i \in k$, new structures, collected in the library $\mathscr{L}_k$. The generation process stops as soon as no further structures are produced. This is checked in row 2.

6.2. Example. The Cope rearrangement and its reaction center graph may be depicted as follows:



Starting from a particular methylbullvalene and this reaction scheme, MOLGEN correctly generates all four methylbullvalenes, for example,



The same result is of course obtained starting with any of the methylbullvalenes. By the corresponding reaction sequence in the parent bullvalene, all 10 CH units are rendered equivalent.

In the following, we shall modify algorithm 6.1 in order to apply it to specific problems.

7. APPLICATION: THE GENERATION OF MASS SPECTROMETRY (MS) FRAGMENTS

Our primary motivation to develop a structure generator working on a reaction network was the request to generate all fragments that occur in a compound's electron impact mass spectrum. Initially, we list a few characteristics of the chemistry that occurs in a mass spectrometer.

(i) The set of reactants consists of a single species: $\mathscr{L} = \{M\}$.

(ii) All reactions have one reactant only.

(iii) The set of reaction schemes consists of two subsets, the set of ionization schemes and the set of fragmentation schemes, $\mathscr{R} = \mathscr{R}_I \dot{\cup} \mathscr{R}_F$.

(iv) In the first step, an ionization is applied to *M*, resulting in a radical cation or (in some cases) a cation plus a radical.

(v) For the further steps, only the cations are of interest.

(vi) After ionization, we can apply an arbitrary number of fragmentations.

For i and ii, no action is required; with respect to the other items, we introduce the following modifications:

• To each reaction scheme, we associate its depth, which says on which level it is applicable. We specify for each reaction scheme an interval of non-negative integers:

$$\text{depth}_{\mathscr{R}}: \mathscr{R} \rightarrow \mathscr{T}(\mathbb{N})$$

where

$$\text{depth}_{\mathscr{R}}(R) = \begin{cases} [1, 1] & \text{if } R \in \mathscr{R}_1 \\ [2, \infty[& \text{else} \end{cases}$$

$\mathscr{T}(\mathbb{N})$ denotes the set of intervals on the natural numbers. This takes into account items iii, iv, and vi.

• With respect to item v, instead of Con( ), we introduce Con^+( )

$$\text{Con}^+(\mathscr{S}) := \{M \in \text{Con}(\mathscr{S}) \mid \text{cha}(M) = 1\}$$

for the decomposition and selection of connectivity components of product graphs. cha(*M*) denotes the sum of charges of the atoms in *M*.

Since there is a single reactant for each reaction, we can restrict attention in line 4 of algorithm 6.1 to $\mathscr{L}_{k-1}$; otherwise, $\text{Prod}_{\mathscr{R}}(\cup_{i\in k}\mathscr{L}_i)$ would produce duplicates only. The modified algorithm, in addition, uses the notion of depth of the reaction schemes that we are going to apply.

7.1. Algorithm. *MolLibMS*($\mathscr{S}$, $\mathscr{R}$, $\text{depth}_{\mathscr{R}}$( ))

(1) $\mathscr{L}_0 \leftarrow \kappa(\mathscr{S})$, $k \leftarrow 0$

(2) **while** $\mathscr{L}_k \neq \varnothing$ **do**

(3) $\quad k \leftarrow k + 1$

(4) $\quad \mathscr{R}' \leftarrow \{R \in \mathscr{R} \mid k \in \text{depth}_{\mathscr{R}}(R)\}$

(5) $\quad \mathscr{L}_k \leftarrow \kappa\,(\text{Con}^+(\text{Prod}_{\mathscr{R}'}(\mathscr{L}_{k-1})))\backslash\cup_{i\in k}\mathscr{L}_i$

(6) $\quad$ *Output*($\mathscr{L}_k$)

(7) **end**

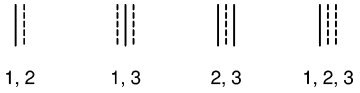
7.2. Example. In order to keep the number of ionization and fragmentation schemes small, we introduce several generic element symbols:

A: any element

Y: heavy atom (i.e., any element except H)

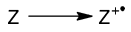
Z: any element bearing a free electron pair (N, O, P, S, and halogens)

Alternatives for bond multiplicities will be coded graphically as follows:

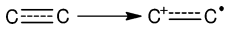


We consider three ionization reactions

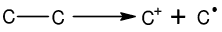
• *n* ionization



• π ionization

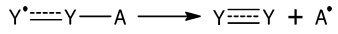


• σ ionization

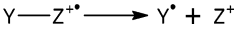


and the following fragmentation reactions

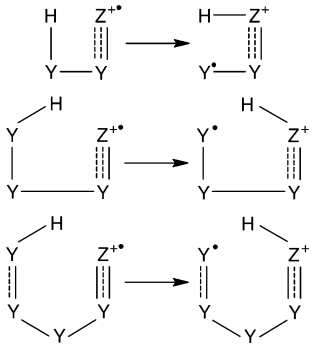
• α cleavage



• σ cleavage



• H rearrangements



Of course, several further reactions can occur in a mass spectrometer. However, this minimalistic set of reaction schemes can already explain many peaks, as seen for the example methyl pentanoate.

Figure 1 shows the MS reaction network for methyl pentanoate obtained by the above reaction schemes. Each square represents an ion; numbers refer to structures in Figure 2. Arrows represent ionization and fragmentation reactions. Labels attached to the arrows denote the reaction scheme applied. Unlabeled arrows represent α cleavages. π ionizations and σ cleavages do not occur in this example.

Figure 2 lists all 32 ions that are generated from methyl pentanoate by the above reaction schemes. There are 16 different molecular formulas and 15 different integer masses occurring in the set of ions. Structures are ordered by decreasing mass. A structure's mass is given in the center of its header together with the molecular formula (left) and the number referred to in Figure 1.

Figure 3 shows an experimental mass spectrum of methyl pentanoate (top), that part of the spectrum explained by our set of MS reactions (middle), and the part unexplained thereby (bottom).

Comparison of the fragments obtained by corresponding reactions from competing structure candidates (e.g., structures isomeric to methyl pentanoate) is an approach to automated structure elucidation via MS.[16,31]

Attempts to quantitatively model the reactions occurring in a mass spectrometer were described earlier.[32−35]

8. APPLICATION: GENERATION OF COMBINATORIAL LIBRARIES

Another important application of reaction-based generation of molecular libraries is the simulation of combinatorial

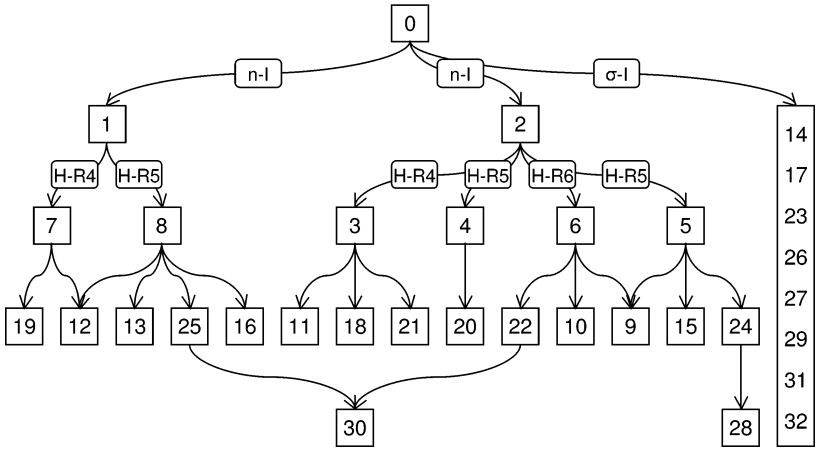


Figure 1. MS reactions of methyl pentanoate.

chemistry. We should be able to generate a library from building blocks and given reactions in order to examine libraries in advance (before or in lieu of synthesis). Often, we find the following situation:

(i) The set of reactants consists of two subsets, a set of central molecules and a set of ligands: $\mathscr{L} = \mathscr{L}_C \dot{\cup} \mathscr{L}_L$.

(ii) Each central molecule can be used just once during the generation procedure, that is, at the very beginning.

(iii) Each reaction product contains at least one central molecule.

(iv) All reactions have one or two reactants.

(v) Reactions between two or more intermediates have to be neglected.

(vi) Stoichiometric side products such as H_2O, HCl, and so forth are to be ignored.

In order to fulfill these conditions, we introduce the following restrictions:

• To each reactant, we associate a depth in which it can occur during the reaction processes. The depth is given as an interval:

$$\mathrm{depth}_{\mathscr{L}} : \mathscr{L} \rightarrow \mathscr{T}(\mathbb{N})$$

where

$$\mathrm{depth}_{\mathscr{L}}(M) = \begin{cases} [0, 0] & \text{if } M \in \mathscr{L}_C \\ [1, \infty[& \text{else} \end{cases}$$

This covers conditions i − iii.

• In order to satisfy condition vi, we use, for the selection of connectivity components in the product graphs

$$\mathrm{Con}^{\geq}(\mathscr{L}) := \bigcup_{M \in \mathscr{L}} \mathrm{Con}^{\geq}(M)$$

where

$$\mathrm{Con}^{\geq}(M) := \{M' \in \mathrm{Con}(M) \mid \mathrm{size}(M') \geq \tfrac{1}{2}\,\mathrm{size}(M)\}$$

Here, size(*M*) means the number of atoms in *M*.

In order to make the algorithm applicable to different functions on the connectivity components, we introduce Con*( ) as an additional argument. For combinatorial libraries, we shall mostly choose

$$\mathrm{Con}^*(\,) = \mathrm{Con}^{\geq}(\,)$$

Conditions iv and v are considered in row 6 of algorithm 8.1.

8.1. Algorithm. *MolLibCC*($\mathscr{L}$, $\mathscr{R}$, $\mathrm{depth}_{\mathscr{R}}(\,)$, $\mathrm{depth}_{\mathscr{L}}(\,)$, Con*( ))

(1) $\mathscr{L}_0 \leftarrow \kappa(\{M \in \mathscr{L} \mid 0 \in \mathrm{depth}_{\mathscr{L}}(M)\})$, $k \leftarrow 0$

(2) **while** $\mathscr{L}_k \neq \varnothing$ **do**

(3) $k \leftarrow k + 1$

(4) $\mathscr{L}' \leftarrow \{M \in \mathscr{L} \mid k \in \mathrm{depth}_{\mathscr{L}}(M)\}$

(5) $\mathscr{R}' \leftarrow \{R \in \mathscr{R} \mid k \in \mathrm{depth}_{\mathscr{R}}(R)\}$

(6) $\mathscr{L}_k \leftarrow \kappa\,(\mathrm{Con}^*(\bigcup_{M \in \mathscr{L}_{k-1}} \mathrm{Prod}_{\mathscr{R}'}(\{M\} \cup \mathscr{L}'))) \setminus \bigcup_{i \in k} \mathscr{L}_i$

(7) *Output*($\mathscr{L}_k$)

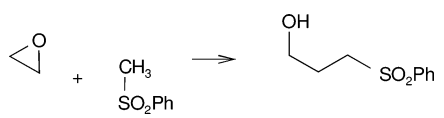
(8) **end**

In certain cases, it is useful to have further tools at hand for the generation of molecular libraries:

• Sometimes, we just want to output the final products, while intermediate ones are not of interest.

• It may also happen that reactants or reaction schemes should occur with prescribed multiplicities. These features are also provided in the MOLGEN reaction module.

8.2. Examples. (a) A sulfone bearing a H atom geminal to the sulfonyl group is able, in the presence of a sufficiently strong base, to open an epoxide in a nucleophilic substitution reaction, forming a new C−C bond. The epoxide oxygen thereby ends up as an alcohol oxygen, for example,



The corresponding reaction scheme may be written as follows:

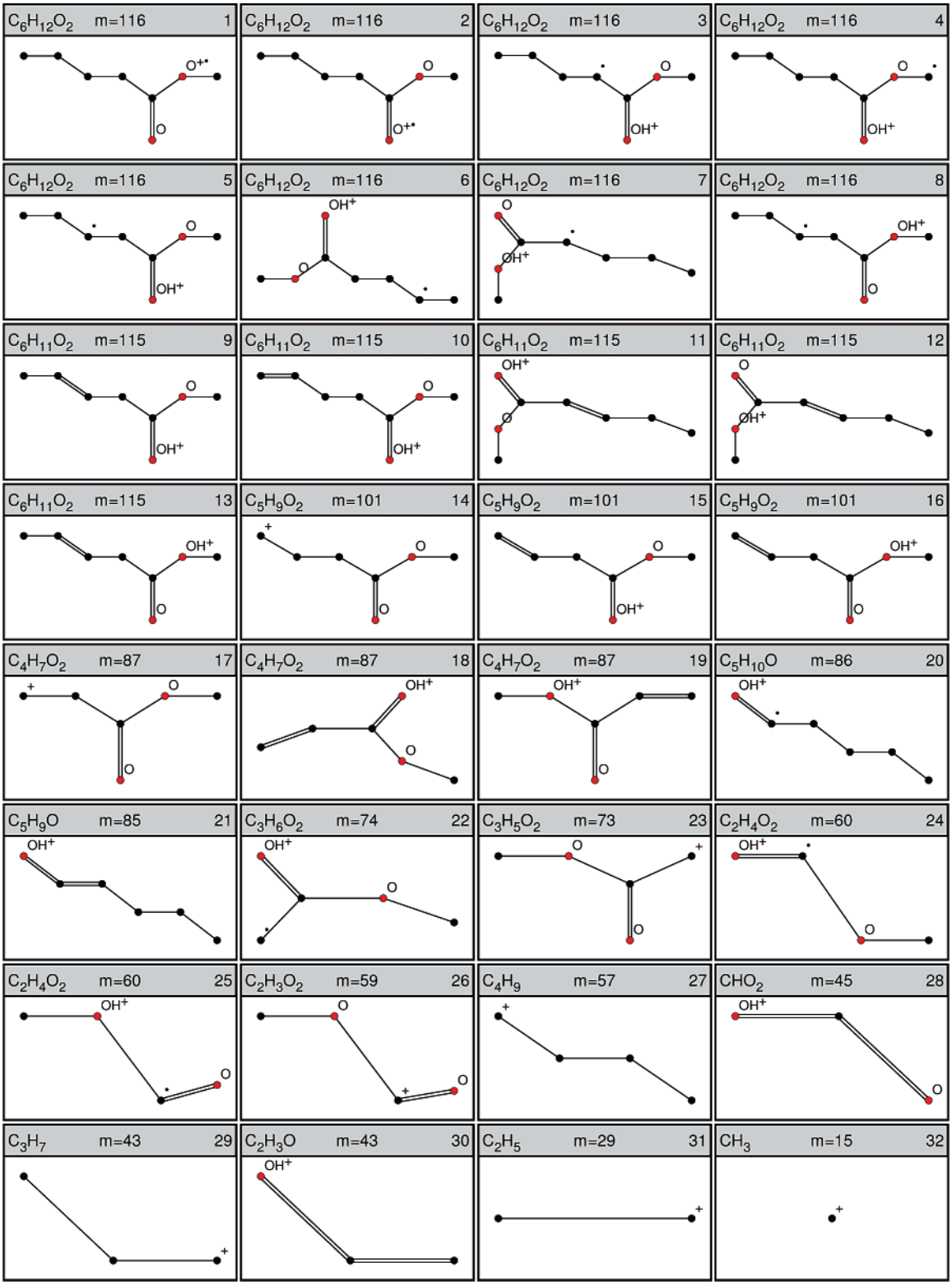
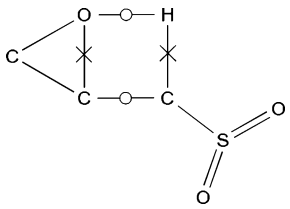


Figure 2. Fragment ions generated from methyl pentanoate.



When this reaction scheme is applied to benzene trioxide, by intramolecular reaction steps, carbocyclic rings may be formed. In fact, given this input, MOLGEN generates 15 products as shown in Chart 1. Of these, **8**−**15** are final products.

Experimentally, many of these types of products were observed to result from reactions of *cis*-benzene trioxide with methyl phenyl sulfone or other acidified methanes.[36−38]

(b) Chemically, for a further ring closure, a good leaving group is required; therefore, we esterify the alcohols formed

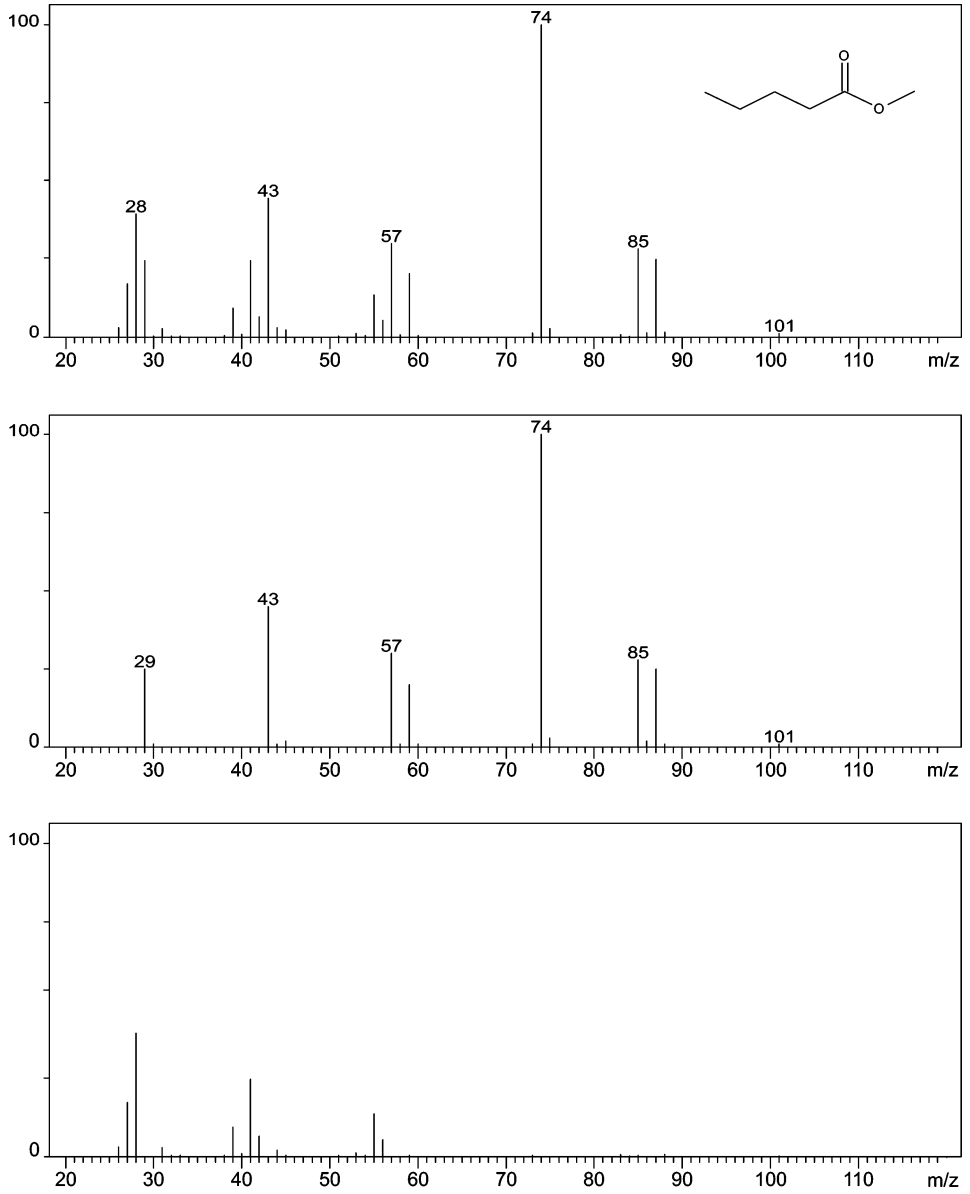
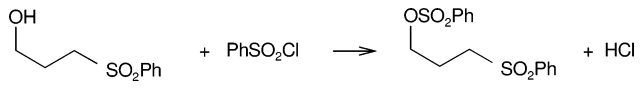
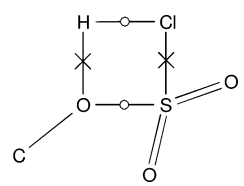


Figure 3. Experimental mass spectrum of methyl pentanoate (top), and the parts of the spectrum explained (middle) and unexplained (bottom) by the reactions considered.

using benzenesulfonyl chloride, for example,

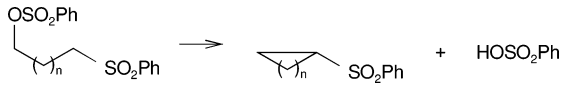


Applying the corresponding reaction scheme

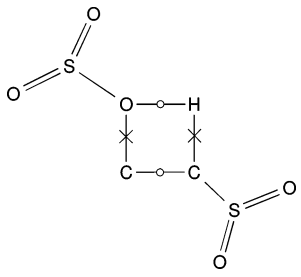


to the above triols **8**−**15**, MOLGEN generates the corresponding tris-benzenesulfonates.

(c) Finally, in the presence of a base, a sulfone bearing an acidic H and a benzenesulfonate leaving group may be cyclized, for example,

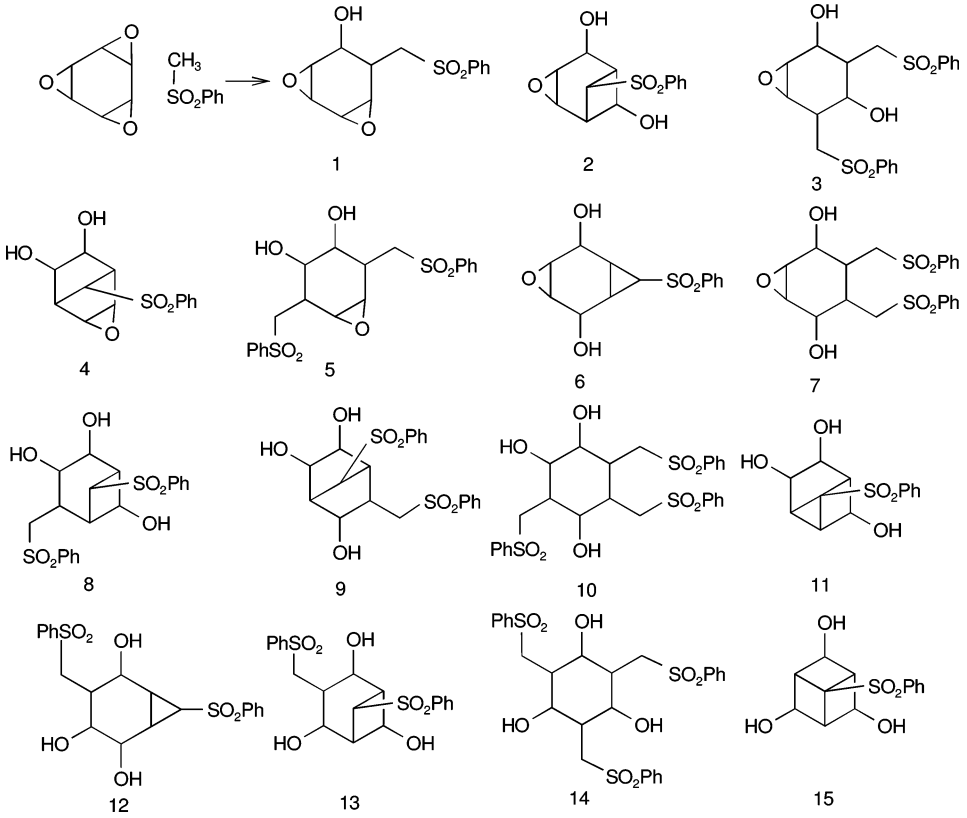


Given the tris-benzenesulfonates of **8**−**15** above and the corresponding reaction scheme

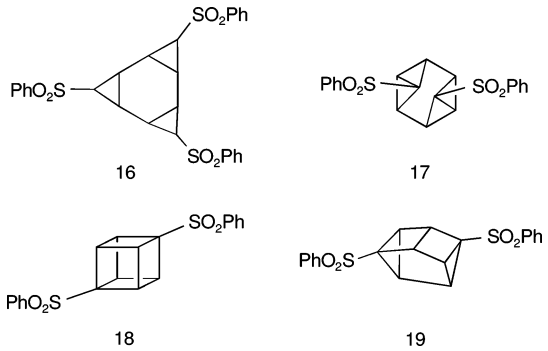


MOLGEN generates carbocyclic tris-σ-homobenzene **16**, disubstituted octabisvalene **17**, disubstituted cubane

Chart 1



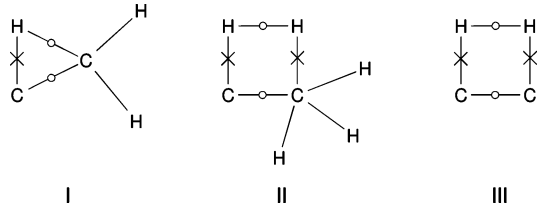
18, and disubstituted cuneane **19** as possible reaction products, as well as some other interesting polycyclics.



In fact, compound **17** was synthesized by this sequence of reactions,[36,37] while analogs of **16** were obtained by a corresponding sequence.[38] Compounds of types **18** and **19**, however, are not observed in vitro nor expected by a chemist. In silico generation of **18** and **19** results from MOLGEN at present not being able to consider the stereochemistry of starting materials and reactions.

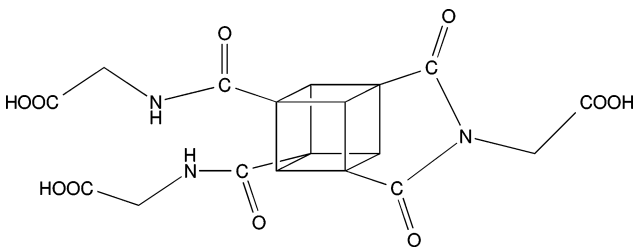
(d) Since MOLGEN is a formal system, we are free to formulate reactions that seem unrealistic, and reactions may be formulated in a very flexible manner. Thus, an equivalent of the above ring closure reaction (step c) may be formulated directly using an alcohol as the reactant instead of a benzenesulfonate. In that manner, products **16**−**19** are obtained without the need to formulate the above esterification reaction (step b).

(e) To demonstrate flexibility, we consider reaction schemes I−III: Starting with methane and methylene, the



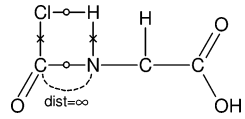
repetitive use of I generates all alkanes via carbene insertions into C−H bonds. The same result is obtained from methane alone and II, the formal condensation of an alkane and a methane molecule with release of molecular hydrogen. Finally, the more general reaction scheme III produces from methane all hydrocarbons (alkanes, alkenes, alkynes, cyclic and polycyclic hydrocarbons, arenes, etc.).

(f) The problem in example 5.1 may also be solved by the network approach. However, the reaction scheme formulated in section 5.1 allows intramolecular reactions, that is, ring closures resulting in products of the following type:



To exclude these kinds of products, a distance restriction is used; that is, the distance between the carbon atom in *A*

and the nitrogen atom in B is set to ∞, which means that these atoms must not be found in the same connectivity component:



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(17) Signs := and =: are defining equal signs. The expression on the colon side is defined by the one on the equal side.

(18) In this notation, the natural number n is recursively defined by $n = \{0, ..., n-1\}$ and Y^X is a standard notation for the set of mappings from the set X to the set Y, $Y^X = \{f: X \rightarrow Y\}$. Here, in order to define molecules consisting of n atoms in $\mathcal{E}$, we take $X = n = \{0, ..., n-1\}$, $Y = \mathcal{E}$, and $Y^X = \mathcal{E}^n$.

(19) The index n of $\mathcal{G}^c_{n,4}$ is the set of (number of) atoms in the molecule, while the second index $4 = \{0, 1, 2, 3\}$ is the set containing all possible multiplicities of covalent bonds. Moreover, the set $\mathcal{G}_{n,m}$ of multigraphs with vertex set n and set of multiplicities m can also be considered as a set of mappings Y^X. We take for X the set $\binom{n}{2}$ of subsets $\{i, j\} \subseteq n$, the set of pairs of vertices, and for Y the set m of admissible multiplicities, since, for $\gamma \in \mathcal{G}_{n,m}$ we can interpret $\gamma(\{i,j\}) = k$ as the existence of a k-fold bond between vertices i and j. Thus, $\mathcal{G}_{n,m} = m^{\binom{n}{2}}$. $\mathcal{G}^c_{n,m}$ means the subset of $\mathcal{G}_{n,m}$ consisting of connected multigraphs.

(20) Recall that $\gamma(\{i,j\})$ denotes the multiplicity of the covalent bond that connects atoms i and j, i.e., $\gamma(\{i, j\}) \in \{0, 1, 2, 3\} = 4$.

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(23) The induced subgraph on the four C atoms under consideration here is the bicyclo[1.1.0]butane graph, since a diagonal bond is not present in cyclobutane but is present in bicyclobutane. This bond does not influence the reaction formalism.

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(25) If desired, the bond between S and O in sulfoxides etc. may be described as a single bond between S(3, 0, 1, 0) and O(1, 3, −1, 0) rather than as the simplistic double bond between S(4, 1, 0, 0) and O(2, 2, 0, 0) used here.

(26) An atom's radical character may or may not be changed in a reaction. It is changed if the atom bears an unpaired electron either before or after the reaction, but not both. The "exclusive or" ($\dot{\vee}$) linking of two logical variables behaves analogously and is therefore used here.

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