The Principle of Minimum Chemical Distance and the Principle of Minimum Structure Change

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Chemical Topology, Structure Correlation, Measure of Chemical Similarity, Quality of Syntheses, Shortest Reaction Pathways

The principle of minimum chemical distance (PMCD) is derived from the general theory of the BE- and R-matrices, and makes precise the vague classical "principle of minimum structure change". In fact, the PMCD may be seen as the principle of minimum structure change in mathematical terms. It provides a quantitative measure of chemical similarity of isomeric molecular systems. Its applications lie in the fields of correlations of substructures, elucidation of reaction mechanisms, and evaluation of synthetic pathways as is illustrated by examples. The mathematical foundations of the computer assisted application of the PMCD are presented.

1. Introduction

The *principle of minimum structure change* [1] is an old and widely used heuristic rule in organic chemistry. Since it has intuitive appeal, and neither its content nor its scope have been explicitly defined, its validity has never been questioned. Some of its more recent corollaries [2, 3] are, however, still under critical discussion [4].

The change in structure which takes place through a chemical reaction involves breaking and making of covalent bonds and a change in the placement of the free valence electrons. The total number $d(E,B)$ of valence electrons which must be shifted in order to achieve the conversion of an ensemble of molecules EM(B) into an isomeric ensemble EM(E) [5, 6] is given by the expression

$$d(E,B) = {}^{(-)}c(B) + {}^{(+)}c(E) + \tfrac{1}{2}[{}^{(-)}f(B) + {}^{(+)}f(E)].$$

Here ${}^{(-)}c(B)$ and ${}^{(+)}c(E)$ are the numbers of the bonds broken in EM(B) and bonds made in EM(E), while ${}^{(-)}f(B)$ and ${}^{(+)}f(E)$ are the numbers of free electrons which are removed from atomic cores in EM(B) and added to atomic cores in EM(E), respectively. Thus $d(E,B)$ appears to be well suited as a quantitative measure for the constitutional changes that occur in a chemical reaction EM(B) → EM(E), and the minimum of $d(B,E)$ corresponds to minimum structure change. The number of valence electrons which are redistributed during a reaction whose beginning EM(B) and end EM(E) are given depends on the correlation of the atoms in the participating EM. When the atoms in EM(B) and EM(E) are identified by indices, this correlation involves stating for each indexed atom in EM(B) its index in EM(E).

For EM with n atoms, the atoms in each EM can be indexed in up to n! different ways. Thus with arbitrary indices the atoms in EM(B) and EM(E) may be correlated in up to $(n!)^2$ different ways. Without guiding theory the trial- and error-search for that correlation of the atoms which corresponds to the minimum $d(E,B)$, and thus minimum structure change, would require the determination of $d(E,B)$ for up to $(n!)^2$ atom onto atom bijections of EM(B) and EM(E).

In Section 2 it will be outlined how an algebraic theory of constitutional chemistry may serve to guide the search for those interconversions of isomeric EM which involve the redistribution of a minimum number of valence electrons. This leads to an algorithm (see Section 3) for determining those

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Abbreviations: BE-matrix = bond and electron matrix; CD = chemical distance; EM = ensemble of molecules; MCD = minimum chemical distance; PMCD = principle of minimum chemical distance; R-matrix = reaction matrix.

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atom onto atom bijections of isomeric EM which correspond to their interconversion by redistribution of a minimum number of valence electrons. The above algorithm has been shown to be useful for the solution of a wide variety of problems in organic chemistry in fields like substructure correlation, the elucidation of reaction mechanisms and the design of syntheses. Examples are discussed in Section 4.

2. Mathematical Framework

Within the framework of a recently published theory of constitutional chemistry [5], ensembles of molecules (EM) are represented by their BE-matrices. The n atomic cores $A_1, \ldots, A_n$ in a given EM are indexed arbitrarily, and the indices of the atomic cores are used as the row/column indices of an $n \times n$ matrix. The entries $b_{ij} = b_{ji}$ $(i \neq j)$ of a BE-matrix are the formal orders of the covalent bonds between the atomic cores A_i and A_j and the entries b_{ii} are the numbers of the free valence electrons belonging to the atomic cores A_i.

The conversion of an EM(B) into an EM(E) by a chemical reaction (or sequence of chemical reactions) is represented by a matrix equation

$$E = B + R$$

where B, E are the BE-matrices of EM(B) and EM(E), and R is a reaction matrix which describes the redistribution of valence electrons during the reaction EM(B) $\rightarrow$ EM(E); the matrix R is a symmetric $n \times n$ natrix with integer entries and with sum over all entries equal to zero. Representing the matrices E, B by points in R^{n^2}, the function

$$d_1(E,B) = \sum_{i,j} |e_{i,j} - b_{ij}| = \sum_{i,j} |r_{ij}|$$

has the properties of a distance, and is called the chemical distance between EM(E) and EM(B) because it is twice the number d(E,B) of valence electrons that are redistributed in the conversion of B to E.

Closely related to this distance, is the ordinary Euclidean distance in R^{n^2},

$$d_2(E,B) = \sqrt{\Sigma |e_{ij} - b_{ij}|^2} = \sqrt{\Sigma |r_{ij}|^2}$$

which does not have the same chemical meaning as the d_1-distance; but there is the relation

$$d_2(E,B) \leqslant d_1(E,B) \leqslant n \cdot d_2(E,B),$$

the first inequality coming from the observation that

$$\sum |r_{ij}|^2 \leqslant \left\{\sum |r_{ij}|\right\}^2$$

and the second from the Schwarz inequality

$$\sum |r_{ij}| = \sum 1 \cdot |r_{ij}| \leqslant \sqrt{\Sigma 1^2 \cdot \Sigma |r_{ij}|^2} = n \cdot \sqrt{\Sigma |r_{ij}|^2}.$$

Since the n atomic cores of an EM can be indexed in up to n! distinct ways, an EM consisting of n atoms is representable in up to n! distinct ways by BE-matrices; any two of these differ by row/column permutations which correspond to the permutations of the atomic core indices. Thus, the BE-matrices are determined by the EM only up to a permutation, in that two matrices B, B′ represent the same EM if there is a permutation matrix P such that $B' = P^t B P$. We shall call the set $\{P^t B P\}$ the cluster determined by B; as we have remarked, all the matrices in a cluster represent the same EM, but with different labellings of the atoms in that EM.

Let EM(B) be convertible into an EM(E); now the minimum chemical distance accomplishing this conversion is to be determined. Due to the non-uniqueness of the representation of EM by BE-matrices, this corresponds to the problem: Find matrices $P^t B P$ and $Q^t B Q$ as close as possible according to their distance; their difference will be a reaction matrix and will fit [6] $Q^t B Q$. That this search requires permuting the row/columns of only one matrix, and that it has at least one solution follows from

Theorem: Let δ_1 (resp. δ_2) be the d_1 (resp. d_2) distance between the clusters $\{P^t E P\}$ and $\{Q^t B Q\}$. Given $i = 1$ or 2, and any member Y of one cluster, there is at least one member X_i of the other cluster such that $d_i(X_i, Y) = \delta_i$.

Proof: Let d (resp. δ) denote d_i (resp. δ_i). Since the clusters are finite sets, there is at least one pair $P^t E P$ and $Q^t B Q$ such that $d(P^t E P, Q^t B Q) = \delta$. The definition of the distance functions d_1, d_2 shows that they are invariant under row/column permutations so, recalling that $Q^t = Q^{-1}$ for permutation matrices, we find

$$\delta = d\,[QP^{-1} E P Q^{-1}, B]$$

and, since $PQ^{-1} = L$ is a permutation matrix with inverse $QP^{-1} = L^{-1} = L^t$ this shows that

$\delta = d(L^tEL, B)$. Using the invariance once again, the assertion follows.

In particular, one can keep B fixed and permute E alone, to find a minimum reaction matrix.

It is immediate from the relation between d_1 and d_2 that

$$\delta_1 \leqslant \delta_2 \leqslant n^2\delta_1 .$$

It need not be true, in general, that $\delta_1 = \delta_2$, or even that an element with minimum d_1-distance to B is to be found among the elements with minimum d_2-distance (see Fig. 1); the possibility $\delta_1 < \delta_2$ could be interpreted as saying that the minimum chemical distance is not necessarily that of lowest energy.

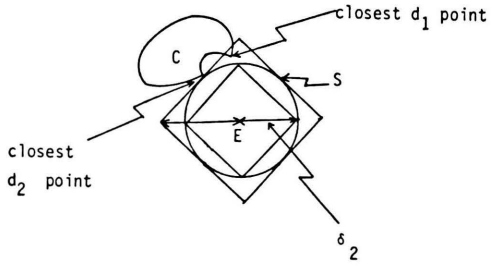


Fig. 1. For a cluster C the point with minimum d_1 distance to E may be different from the point with the minimum d_2 distance.

Although a member of the cluster of E having minimum d_1-distance to B is required for the chemical problem, the computational techniques are better adapted to finding members of the cluster having minimum d_2-distance to B. Notice that finding δ_2 does provide a rough bound for δ_1 (from which it is frequently possible to determine δ_1) and, for the sake of completeness, we present two known techniques for computing δ_2.

Let $\langle \cdot, \cdot \rangle$ denote the inner product in R^{n^2}. All the points P^tEP lie on a d_2-spheres (which is a convex set).

Theorem

$$||B - P_0^tEP_0|| = \inf_Q ||B - Q^tEQ|| \text{ if and only if}$$

$$\langle B - P_0^tEP_0, Q^tEQ - P_0^tEP_0 \rangle \leq 0 \text{ for all } Q^tEQ$$

Proof

"$\Leftarrow$:"

$$||B - Q^tEQ||^2 =$$
$$= ||(B - P_0^tEP_0) - (Q^tEQ - P_0^tEP_0)||^2$$
$$= ||(B - P_0^tEP_0)||^2 -$$
$$- 2\langle B - P_0^tEP_0, Q^tEQ - P_0^tEP_0 \rangle$$
$$+ ||Q^tEQ - P_0^tEP_0||^2$$
$$\geq ||B - P_0^tEP_0||^2$$

so $||B - P_0^tEP_0||$ is indeed minimum.

"$\Rightarrow$":

For every $0 < \lambda \leq 1$ and every Q^tEQ we have

$$||B - P_0^tEP_0||^2 \leq$$
$$||B - [(1-\lambda)P_0^tEP_0 + \lambda Q^tEQ]||^2 =$$
$$||(B - P_0^tEP_0) - \lambda(Q^tEQ - P_0^tEP^t)||^2$$

so

$$0 \leq -2\lambda\langle B - P_0^tEP_0, Q^tEQ - P_0^tEP_0 \rangle +$$
$$\lambda^2 ||Q^tEQ - P_0^tEP_0||^2 .$$

Since this must hold for all $\lambda > 0$, the required conclusion follows.

For the computational solution of the problem the following theorem is particularly important.

Theorem

$$||B - P_0^tEP_0|| = \inf_Q ||B - Q^tEQ|| \text{ if and only if}$$

$$\langle B, P_0^tEP_0 \rangle = \max$$

Proof

By the law of cosines

$$||B - Q^tEQ|| = ||B||^2 + ||Q^tEQ|| -$$
$$- 2\langle B, Q^tEQ \rangle$$

so that since $||Q^tEQ||$ is constant for all Q, the distance will be minimum whenever the inner product is maximum.

3. The Algorithmic Solution of the MCD Problem

3.1. Different approaches

We formulate the minimization of the chemical distance d_1 as a nonlinear minimization problem G:

$$G(P, Q) = d_1(PEP^T, QBQ^T) = \min \qquad (1)$$

Permutation matrices P, Q must be found such that the chemical distance between the starting and target molecule B and E with permuted atomic indices becomes minimal.

As shown in Section 2, it is, however, sufficient to seek the minimum of the function

$$F(P) = d_1(PEP^T, B) = \min \qquad (2)$$

The only direct way known so far to solve (2) is a trial and error search (complete enumeration), *i.e.*,

to determine F for all possible n! permutation matrices P. Since (10!) is already 3,628,800, this method is limited to very small MCD-problems and thus is in general not applicable.

It is also possible to consider the MCD-problem from a graph theoretical point of view. The graphs of B and E must be matched with minimum breaking and making of bonds, *i.e.* one must find a common indexing of the atoms in B and E such that in the graphs of B and of E a minimum number of bonds must be broken in order to obtain isomorphic graphs.

This implies that we have to match the atoms of as *many* as possible common largest substructures of B and E. This is however *not* equivalent to the process consisting of matching the atoms of the largest substructure of B and E, then the atoms of the next largest substructure and so forth. This is demonstrated by the following example:

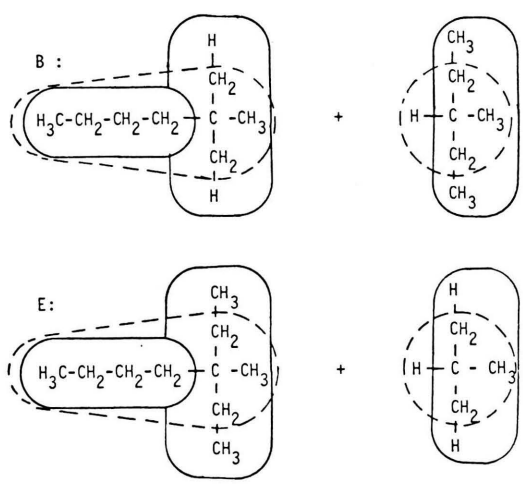


Fig. 2.

(I) (II) first and second largest common substructure of B and E (CD = 8);

substructures which occur at an assignment of the atoms according to MCD (CD = 4).

Thus, for the problem at hand, common substructure search algorithms alone do not suffice to determine that correspondence of the atoms of B and those of E which yields the MCD.

The approaches described above are applicable only either to MCD problems of small EM or for generating suboptimum solutions by matching the largest substructures. Thus we had to reformulate the problem for obtaining an optimum solution:

Let $\tilde{H}$ be the problem:

$$\tilde{H}(P) = d_2(PEP^T, B) = \min \tag{3}$$

The minimization of $\tilde{H}$ is equivalent to the maximization of H or the minimization of —H (see Section 2)

$$\begin{aligned} H(P) &= PEP^T \cdot B = \max \\ -H(P) &= -PEP^T \cdot B = \min \end{aligned} \tag{4}$$

Here · denotes the scalar multiplication of two matrices.

According to Section 2, the set of optimum solutions of (2) is a subset of the set of optimum solutions of (3) and (4), respectively. Since we are able to detect the optimum solutions of (4), we only need scan these (normally very few) permutation matrices for satisfying condition (2).

There exist several algorithms for the minimization of (3). They all were originally developed for problems of operations research like the optimum assignment or the backboard wiring problem [7]. All of these algorithms are non-iterative and work as branch-and-bound algorithms. They vary mainly in the determination of upper and lower bounds for the optimum solution of H.

We decided to use the perturbation method recently developed by R. E. Burkard [8, 9] which is probably the most powerful approach. We modified this branch and bound algorithm to suit our chemical applications.

3.2. The MCD-algorithm

To describe the algorithm, we change from the matrix notation of a permutation matrix P to the automorphism notation π of a permutation:

$$\pi\colon \{1, \ldots, n\} \to \{1, \quad, n\}$$

The optimization problem (5) then presents itself in the following form:

$$H(\pi) = \sum_{i,j=1}^{n} e_{\pi(i)\pi(j)}\, b_{ij} = \max \tag{5}$$

A branch-and-bound algorithm partitions the original problems into several subproblems ("branching") and attempts to close in on the optimum solution by determining upper and lower *bounds* of these subproblems.

3.2.1. The branching

For describing the algorithm in more detail, we introduce a partial permutation π_M:

Let $N = \{1, \ldots, n\}$. For any set $K < N$ we define
$\pi_M := \{i, \pi(i))\} \quad i \in M$

Then the subproblems comprize the determination of permutations π_M with certain fixed assignments $i_k \rightarrow j_k$. Thus a decision tree is generated:

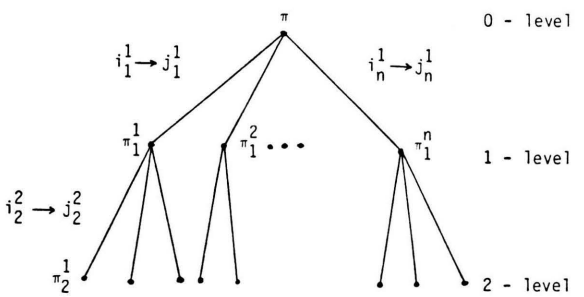


Fig. 3. Decision tree of the MCD-algorithm. Each node corresponds to a subproblem. The higher the level of the tree, the smaller the subproblem. For each node of the tree (which corresponds to a specific subproblem and partial permutation, respectively) a lower and upper bound for all solutions including this partial, permutation can be calculated.

For any particular node of the tree (according to Fig. 3) we can calculate an upper and lower bound for all subproblems having this node as a root. The lowest upper bound is stored away during a run. If a lower bound of a given problem at some node happens to be higher than the lowest upper bound thus far detected all branches starting from this node to higher levels can be cut off from the decision tree since they cannot lead to an optimum solution. It is therefore essential to have a method which finds rather precise lower and upper bounds at low levels (first or second) in order not to be forced to work "deep" into the decision tree.

3.2.2. Detection of bounds

The detection of the bounds is illustrated by the original problem (4) (root of the decision tree) but applies in the same way to any other node of the decision tree except that the dimension has to be changed.

From the bond matrices B, E so-called [9, 10] cost matrices C^{ip} are constructed according to

$$C^{ip} = (e_{ip} b_{iq})_{i,q=1,\ldots,n} \quad i, p = 1, \ldots, n$$

These symmetric cost matrices are arranged in a block matrix $(C^{ip})_{i,p=1,\ldots,n}$. It can be shown [8], that the diagonal elements C^{ii} of this block matrix can be considered as a linear assignment problem [10] whose solution forms a *lower bound* to all those nodes of the decision tree, starting from this problem to lower levels. The other matrix elements are considered to be "pertubations", and it is attempted to delete them by matrix transformations before solving the linear assignment problem. Since the solution of this linear assignment problem does not only give a numerical value, the lower bound, but also a permutation belonging to this value, an *upper bound* for all nodes starting from this problem can be evaluated by calculating

$$\sum_{i,j=1}^{n} e_{\pi(i)\pi(j)} b_{ij} .$$

The constitutional symmetry [11] of B and E allows the cutting off of additional branches of the decision tree, thereby avoiding redundant treatment of permutations which are equivalent due to constitutional symmetry. The determination of symmetry has to be repeated on each level since the partial permutations (*i.e.* the fixed assignment) can prohibit the free choice of an arbitrary assignment from among originally symmetrical assignments. With highly symmetrical molecules this technique provides a powerful tool for rapidly progressing through the decision tree by avoiding symmetry equivalent solutions. After working through the decision tree, the lowest upper bound is the optimum solution.

3.2.3. The program

The PMCD program is written in FORTRAN and consists of about 2000 statements. It can handle chemical systems with up to 36 multivalent atoms each for starting and target EM. For ensembles with not more than 15 to 20 multivalent atoms of the same chemical element optimum solutions (complete work through the decision tree) can be found with reasonable CPU time (≤ 5 min on a Cyber 175). For example a problem with 10 C- and 10 O-atoms can be solved much faster than a problem where only 15 C atoms are considered since the latter problem involves working through a decision tree with 15! nodes while the first problem involves only $2 \times 10!$ nodes. This also shows that the CPU time

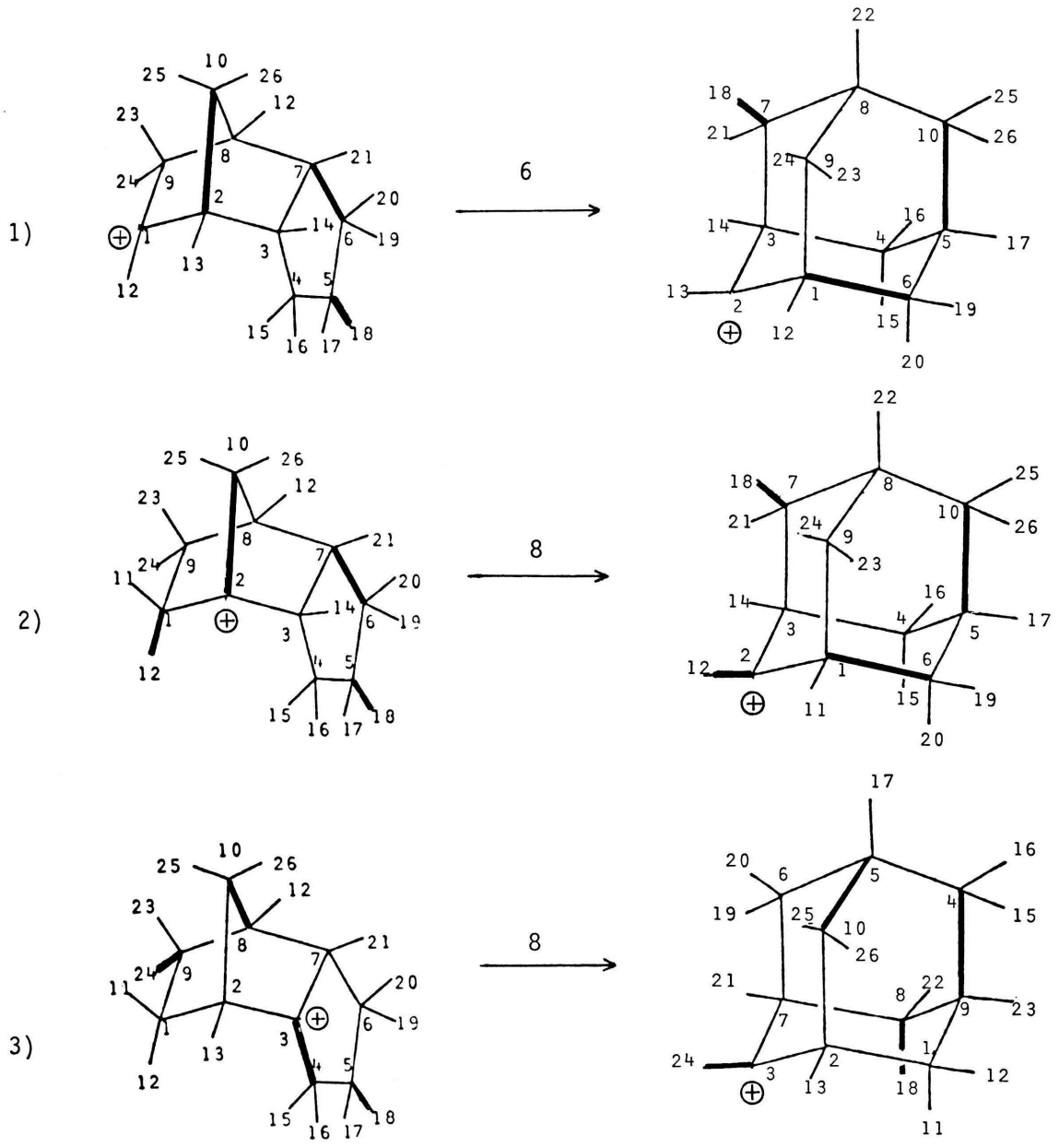
increases very fast for bigger problems since the algorithm is of class NP, *i.e.* it works with polynomi ally increasing time on nondeterministic Turing machines [12, 20].

4. Applications of the PMCD

An atom by atom correlation of isomeric ensembles of molecules is useful for the solution of many chemical problems such as the search for substructures, the elucidation of reaction mechanisms and the evaluation of synthetic pathways.

The application of the principle of minimum chemical distance will be illustrated by a few examples which are chosen from the field of mechanistic studies and synthesis [13]. The correlation of the atoms in the starting materials and products of

Table I. The minimum CD between the carbonium ions of tetrahydrodicyclopentadiene (**1**) and the carboniums of adamantane (**2**) (bonds broken and made in bold face).



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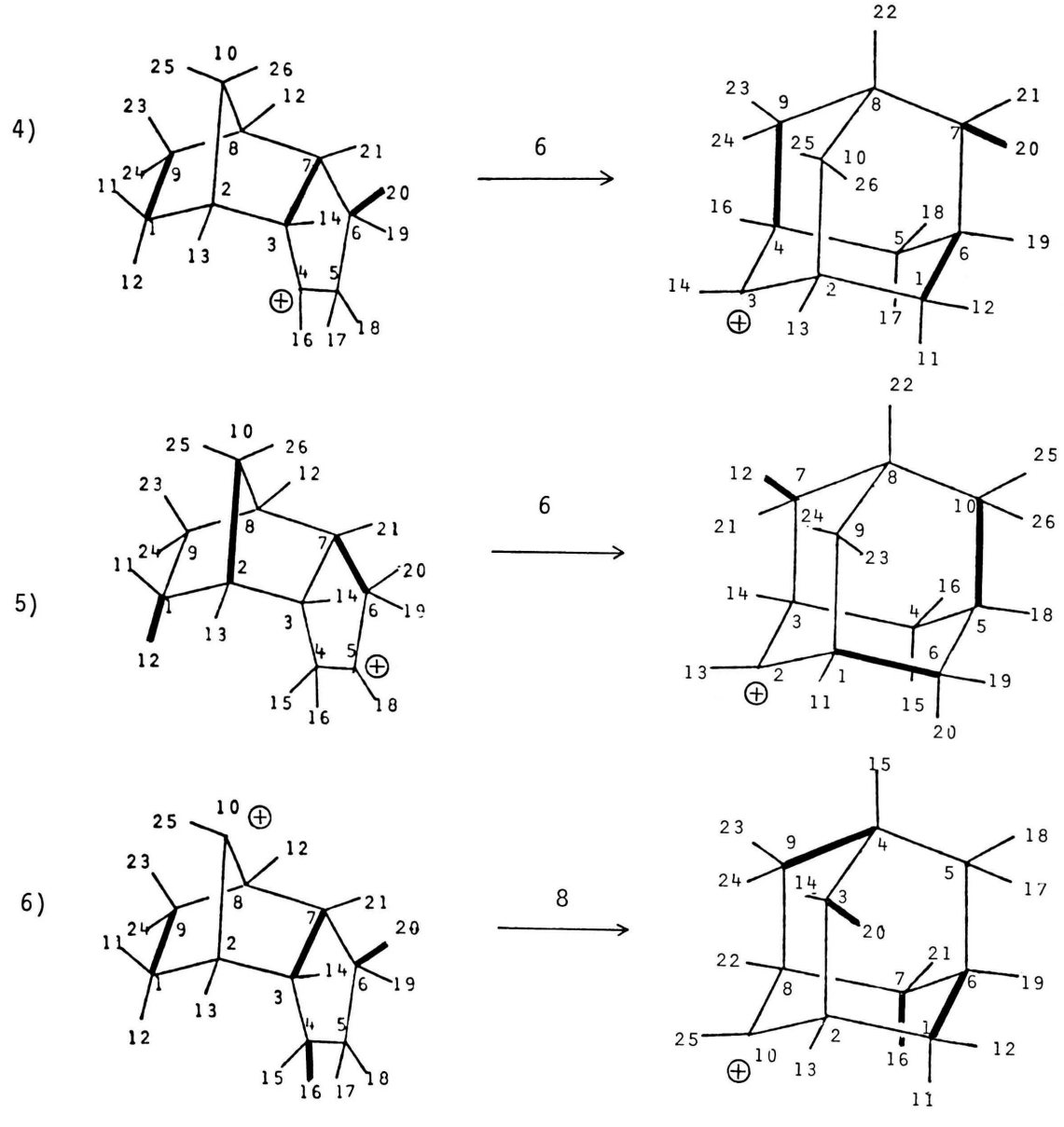

a reaction depends on the mechanism, and conclusions can be drawn about a reaction mechanism if one knows for each atom in the products the corresponding atom in the starting materials. This is the basis for isotopic labelling experiments in the study of reaction mechanisms. With the PMCD program all involved atoms may be traced according to MCD.

The MCD of a reaction is a measure for its mechanistic complexity because it is twice the minimum number of electron shifting arrows which are needed to achieve the result of a chemical reaction. For a given overall reaction more than one mechanistic pathway may exist with the same CD.

Chemical reactions as sequences of elementary steps are treated here as overall processes and their

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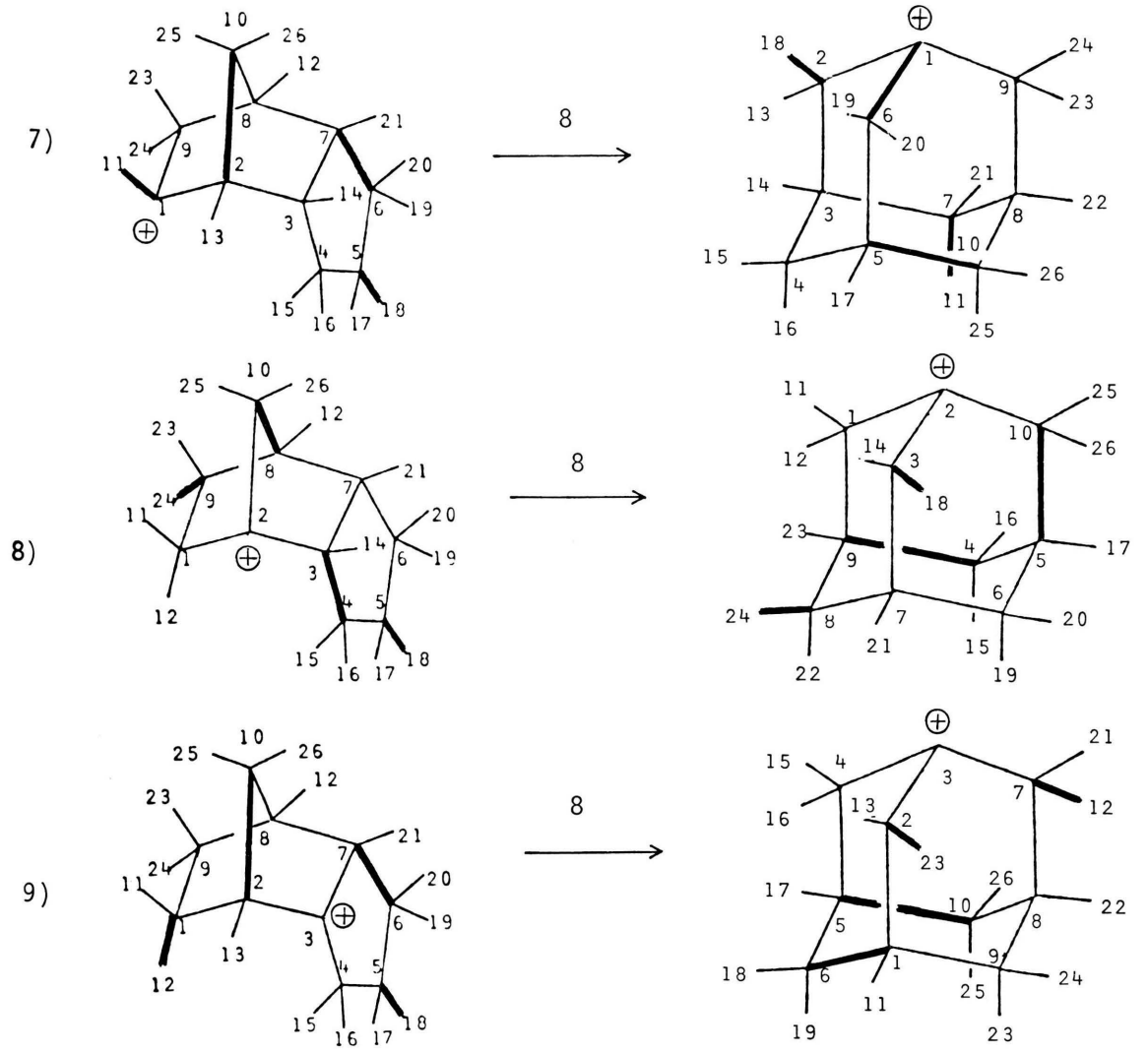
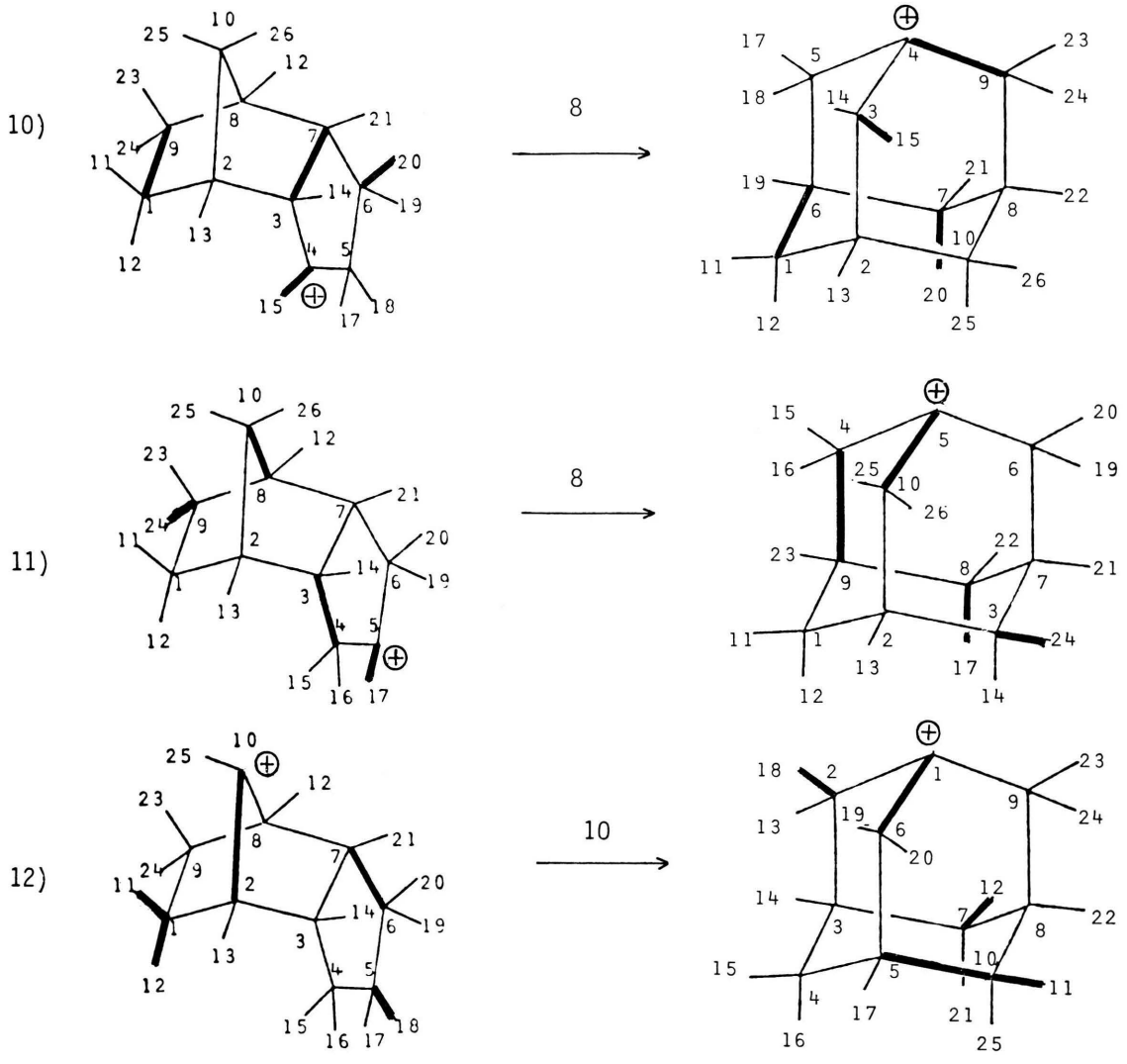


CD corresponds to an overall displacement of electrons. The number of valence electrons which have participated in a chemical process may be larger than is seen in the chemical change determining the CD. The higher the number of elementary steps the more the reaction may deviate from pathways of MCD. However, even then the number of valence electrons shifted deviates only slightly from the MCD.

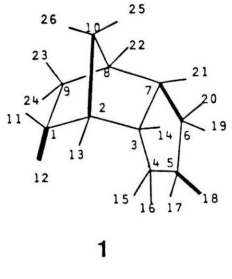
In some cases a reaction pathway with MCD may not be feasible due to energetic reasons, e.g. stereochemical constraints. Then, a non-minimum pathway will be followed with a preference for low chemical distances.

The conversion of tetrahydrodicyclopentadiene (**1**) to adamantane (**2**) proceeds directly from the starting material to the product [14] although undoubtedly a multistep sequence of rearrangements must take place. The mechanism of this reaction is still under investigation. Whitlock *et al.* [15] proposed a network of conceivable pathways which consists of 1.2-shifts only. One of these pathways was given preference by Schleyer on the basis of molecular mechanics calculations [16]. The

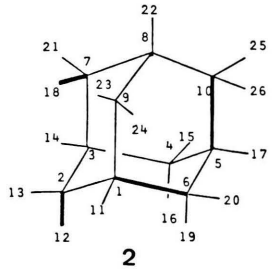
Table I (continued).



"shortest" paths of Iizuka *et al.* [17] are not the shortest according to MCD but they involve the minimum number of specified steps.



1



2

The PMCD provides a new way of looking at this problem. Beginning with an arbitrary indexing of the atoms of tetrahydrodicyclopentadiene (**1**) the indexing of adamantane (**2**) corresponds to an MCD of eight. Thus if the reaction proceeded from hydrocarbon to hydrocarbon, the bonds indicated in bold face in **1** would be broken and the one in **2** would be made. In comparison the sum of the CD of the individual steps of the shortest pathway which has been previously considered by Schleyer [16] is 20.

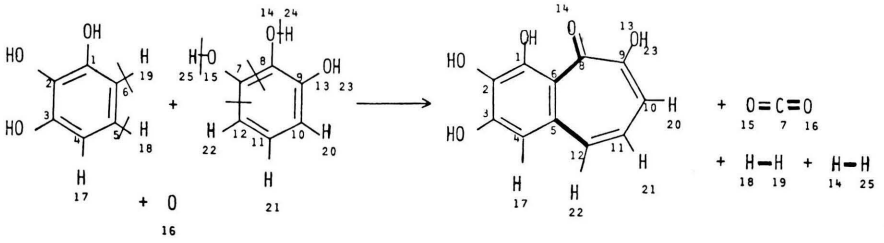
Since it is plausible to assume that the reaction involves the intermediacy of carbonium ions we

compared the minimum CD of the 12 conversions which lead from one of the six isomeric carbonium ions of **1** to one of the two carbonium ions of adamantane.

Interconversion of the hydrocarbons requires the involvement of two more bonds than the interconversion of the carboniumions. Thus a minimum CD of six for the carboniumions can be expected. This minimum is found only for the rearrangements 1, 4 and 5. It is noteworthy that all pathways with a minimum CD of six lead from a secondary carboniumion of **1** to a secondary carboniumion of **2**. In each one of these cases the secondary carboniumion center in **2** corresponds to an initially tertiary carbon atom in **1**.

Purpurogallin is formed in a quite unusual reaction by oxidation of purpurogallol. A mechanism for this reaction has been proposed by Horner [18]. The fate of the individual atoms and the breaking and making of bonds for the overall conversion according to this proposed mechanism is indicated in the following scheme:

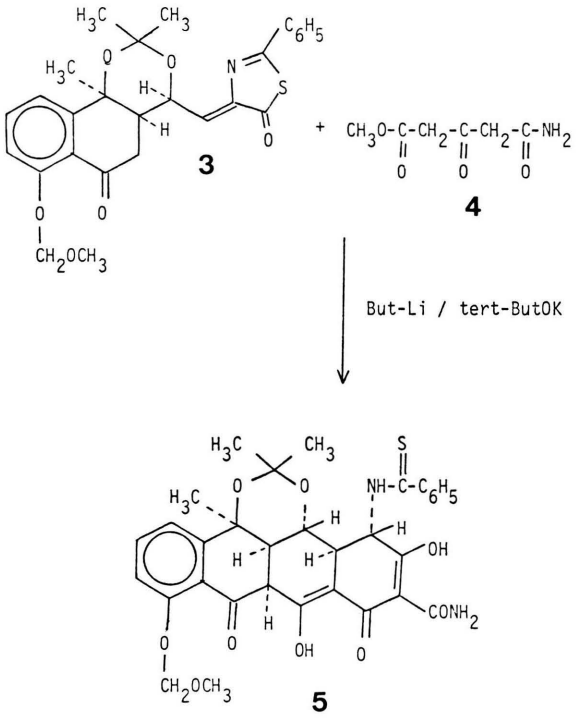
Scheme 1.



The chemical distance for this overall change is 32 since two free electrons (on the oxygen atom) are consumed, seven bonds are broken and eight bonds are made. A study of this reaction with the PMCD program gave the same results: The atom to atom matching is again the one indicated in Scheme 1 and the CD is 30. Thus the proposed mechanism for the formation of purpurogallin proceeds along the path of MCD.

A key step in the synthesis of terramycine by Muxfeldt *et al.* [19] was the condensation of the tetracyclic precursors (**3**) with the β-ketoester (**4**) to the pentacyclic structure (**5**) (Scheme 2).

Scheme 2.



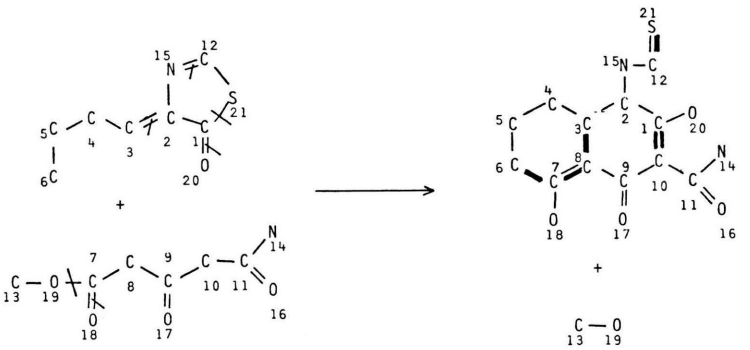
The condensation was accompanied by a rearrangement of the thiazolone ring structure. The essential constitutional features of this condensation and rearrangement process are contained in Scheme 3.

The chemical distance for this conversion is 24. This is also the minimum chemical distance found by the MCD program.

5. Conclusion

With the PMCD the classical principle of minimum structural change is put on a quantitative basis.

The principle of minimum structural change has been successfully used in an intuitive fashion throughout the history of chemistry. This intuitive approach involves implicitly a correlation of atoms and bonds in different molecular systems. Even if defined sufficiently precisely the principle of minimum structure change could not be practically adapted to a corresponding computer assisted correlation of structures because computers due to their



Scheme 3.

lack of intuition, would be able to solve problems only by exhaustive trial and error. This would limit application of the principle to fairly small systems because computation time would increase factorially with the number of atoms involved.

It is not only the more precise definition of the PMCD which makes it work in the computer assisted solution of chemical problems but also its mathematical basis, and the metric of the representation space in which chemical problems may be embedded in order to be solved. Of particular importance is the fact that the minimum of CD can be found by the minimum of Euclidean distance between the points which represent the given ensembles of molecules.

Furthermore, the solution of such problems has become possible through progress in operations research, in particular, the development of powerful nonlinear integer optimization algorithms.

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[20] *Note added in proof:* A. v. Scholley and J. Brandt will soon report on a new, substantially more efficient version of the PMCD program which is based on an improved branch and bound program by R. E. Burkhard and coworkers.