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IGOR and Computer Assisted Innovation in Chemistry

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In memoriam James Dugundji

IGOR (Interactive Generation of Organic Reactions) is the first general-purpose, artificial-intelligence-type computer program for generating graphic representations of unprecedented chemistry. The unique capabilities of IGOR are based on a global mathematical model of the logical structure of chemistry and an analysis of the complete combinatorial set of conceivable solutions to a problem by means of a converging interactive hierarchic classification procedure that avoids heuristic selection rules, because of their arbitrary nature and lack of general validity. The potential role of artificial intelligence methods in innovation by creative research is discussed in the context, as are the criteria for novelty in chemistry. The scope and limitations of IGOR are illustrated by some applications; the elaboration of new reactions with the aid of IGOR and their experimental realization are presented.

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1. Creativity and Innovation

Creativity and innovation in science begin with the production of new information which does not follow directly from known data, e.g. by numerical calculations according to a fixed recipe, or by retrieval and simple manipulation of stored data. The highest level of creativity in science is encountered where new problems are recognized and formulated. Which level of creativity is the upper bound for computer-assistance?

Numerical computations as well as the storage and retrieval of data are the traditional uses of computers in chemistry and other sciences. In the past two decades so-called artificial intelligence (AI) programs have entered chemistry. Complex logical operations, sophisticated data manipulation, problem-solving and decision processes are among the characteristic operations of AI-type programs. Is it possible to endow such computer programs with creativity and the capability of innovation? If artificial intelligence cannot replace human creativity, can it at least be used to augment it? Such and related questions are under serious discussion today, not only from a scientific and technical standpoint, but also from a philosophical view[1].

There are probably no generally valid answers to these questions. The role and potential for creativity of artificial intelligence varies from discipline to discipline and from case to case. Even in science and technology it is difficult to define its prerequisites, innovation and creativity. It seems easier to exclude the non-innovative on an ad hoc basis. The ability to generate novel unprecedented information, though a necessary criterion for creativity, is not in itself sufficient.

For example, a random-number generator can produce unprecedented data, but it is certainly not creative. Patents are only granted for inventions that represent an innovation. The conceivable straightforward accomplishments of a hypothetical average specialist who lacks creativity but has access to the literature are often cited in order to characterize what are considered to be noninnovative achievements.

It may be that this hypothetical average specialist represents the upper bound for the so-called artificial intelligence of computers. Nevertheless computers are most definitely capable of augmenting a human being's creativity, not only by relieving him of menial chores, computations, and data handling, but also by virtue of their combinatorial and logical problem-solving and decision making capabilities, and even the ability to lead into new problems. With suitable conceptual foundations and well-designed man/machine interaction, the contributions of computer assistance to creativity and innovation may become significant, in particular in chemistry. The proportion of the contributions to creativity by man or machine may vary considerably from case to case.

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2. Computer Assistance in Chemistry

There are many important chemical problems whose «unknown» is a molecular system or a chemical reaction. In general they have a combinatorial multitude of conceivable solutions. Such problems are encountered in the design of syntheses, the development of new reactions, the prediction of products which may be obtained from given reactants, and in industrial chemical research, where one tries to find chemical compounds embodying certain desirable properties and lacking other, undesirable properties.

Chemistry is an empirical science and, as a rule, chemists solve such problems through analogist's reasoning, using their empirical knowledge, experience, chemical intuition, and often plain luck. A creative and ingenious chemist finds a good solution to a chemical problem among the many conceivable solutions without much trial and error, often a solution which has some perplexing features to the average colleague.

Being aware of the combinatorial aspect of chemical reactivity, *Stevens* and *Brownscombe*[2] developed a computer program for generating analogs of the retro-ene reaction and other pericyclic reactions with four to six reactive centers through permutation of the chemical elements and interatomic bonds at the reactive centers. Enthalpy estimates were used as a selection criterion. This program is a milestone in computer chemistry, because it is the first computer program with some capability of «creating» unprecedented chemical reactions.

The well-known and successful reaction-library-based computer programs for the design of syntheses[3] have much less «creativity». They generate divergent trees of synthetic pathways by retrieval and manipulation of data on known chemical reactions that are stored in the reaction library. The trees are pruned by the operator in an interactive mode, or by automatic application of heuristic selection rules. The resulting synthetic pathways are sequences of known reactions.

Chemical documentation and quantum chemical computations are the most widespread and best-known applications of computers in chemistry. Advances in theoretical physics and mathematical methods as well as progress in computer hardware and software technology enable the quantum chemists to calculate many properties of molecules with great accuracy. The results thus obtained are indispensable for chemistry; in particular, the correlation of the structural features of molecules with a great variety of spectroscopic data would be inconceivable without the results of quantum chemistry[4]. This discipline has also been remarkably successful in the detailed physical interpretation of simple chemical reactions. Quantum chemistry has also provided guidelines for the interpretation and prediction of the stereochemical course of some complex chemical reactions. The Woodward-Hoffmann rules are a glamorous example[5]. However, this kind of theoretical chemistry is, in essence, the theoretical physics of molecules, and its applications are confined to given individual molecules and their reactions. The combinatorial multitude of molecular systems is still beyond the scope of quantum chemistry, because it is not possible to compute and analyze a complete energy hypersurface of any chemically relevant collection of atoms[4, 6]. The computations of quantum chemistry follow certain computational recipes, and their «chemical creativity» is generally limited to a variation of nuclear coordinates. The chemical creativity of computer programs in quantum chemistry derives exclusively from the human beings that use them. Quantum chemistry has not yet tapped the creative problem-solving AI capabilities of the computers.

3. The Logical Structure of Chemistry and a Unified Theory of Chemistry

The use of a language requires knowledge not only of its vocabulary, but also of its grammar and syntax that represent its logical structure. In chemistry we have an abundance of vocabulary in terms of various types of detailed information on chemical systems, their behaviour, and properties, but we do not use any universal grammar or syntax. At best, some general principles and fragmentary «local» models and representations of the logical structure of chemistry are available. In the solution of a great variety of chemical problems – especially with computer assistance – a qualitative global theory of the logical structure of chemistry could provide helpful «grammatical guidance».

Knowledge of the logical structure of chemistry is important for a systematic approach to chemical problems with a combinatorial multitude of conceivable solutions. The logical structure of chemistry has a constitutional aspect and as a «fine-structure», also a stereochemical aspect[7]. The logical structure of stereochemistry can be described by the theory of chemical identity groups[8], whereas the logical structure of constitutional chemistry is representable in terms of the theory of the BE and R-matrices[9], the so-called DU-theory[10]. In essence, this theory is derived from valence bond theory. Axiomatic to this theory is the idea that a covalent chemical bond corresponds to a pair of valence electrons that is shared by two atomic cores (atomic nuclei cum inner electrons), an extension of the concept of isomerism from molecules to ensembles of molecules (EM), and a twentieth century corollary of the classical principle of conservation of matter, namely that the total numbers of valence electrons and atomic cores are conserved during chemical reactions[11].

An EM may consist of one, or many molecules; these may be chemically identical or chemically different. The gross empirical formula of an EM indicates the kind and number of atoms that are contained in the EM, whereas the detailed empirical formula consists of the empirical formulas of the molecules that belong to the EM. Distinct EM having the same gross empirical formula are called isomeric EM. They may differ constitutionally or stereochemically.

Let **A** be a given collection of atoms. An EM(**A**) is any molecule or EM that can be formed from **A** using each atom belonging to **A** exactly once. An FIEM(**A**), the family of isomeric EM of **A**, is the set of all EM(**A**). The chemistry of **A** is common to all members of FIEM(**A**). A theory of the FIEM(**A**) such as the DU-theory is valid for all of chemistry, since **A** can be any collection of atoms, and the solutions to any chemical problem can be imbedded in the chemistry of some FIEM(**A**)[9].

Within the framework of this theory an EM is described by its BE-matrix; it is equivalent to the constitutional formula of the EM.

The BE-matrix $B = \langle b_{ij} \rangle$ of an EM(**B**) with n atoms $A_1 \ldots A_n$ is a symmetric ($b_{ij} = b_{ji}$) n × n matrix with integer non-negative entries. The rows/columns are assigned to the cores of the indexed atoms.

The off-diagonal entries b_{ij} ($i \neq j$) in the i-th rows and j-th columns of a BE-matrix B are the formal bond orders of the covalent bonds between the atomic cores A_i and A_j. The diagonal entries b_{ii} are the numbers of the lone valence electrons at the A_i.

Any two BE-matrices B and B' are equivalent and represent the same EM(**B**), if they are interconvertible by row/column permutations, corresponding to permuted atomic indices, i.e. if $B = PB'P^{-1}$ (P being an n × n permutation matrix). Thus an EM is represented by up to n! equivalent BE-matrices[12].

A one-to-one correlation of molecules and their BE-matrices is needed for documentation purposes. This is best accomplished by uniquely indexing the atoms in the molecules by the algorithm CANON[13]. The CANONical atomic indices account for constitutional symmetries[7, 13], and they are also well-suited for stereochemical documentation[8]. Thus CANON provides an «interface» between constitutional chemistry and stereochemistry.

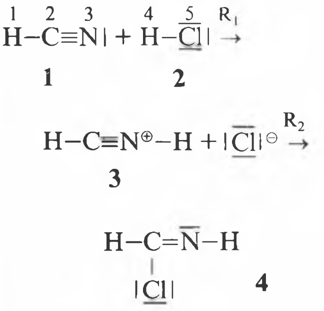
An EM of m molecules can be described by BE-matrices containing m blocks along the main diagonal. These blocks represent the individual molecules in the EM.

A chemical reaction is always the conversion of an EM into an isomeric EM. A chemical reaction EM(**B**)→EM(**E**) is represented by a transformation $B \rightarrow E$ of the BE-matrix B of the educt EM(**B**) at the beginning of the reaction into E, the BE-matrix of the products EM(**E**) at the end of the reaction. This transformation is best executed by adding a reaction matrix $R = \langle r_{ij} \rangle$ to the beginning matrix B, according to $B + R = E$, the fundamental equation of the theory[9]. The n × n symmetric R-matrix indicates the changes in the distribution of bonds and lone electrons by the reaction. The off-diagonal entries r_{ij} tell which covalent bonds are broken ($r_{ij} < 0$), or made ($r_{ij} > 0$) during the reaction; the diagonal entries r_{ii} correspond to the changes in the number of lone electrons at A_i. In fact, an R-matrix corresponds to a pattern of «electron shifting» arrows.

Since the matrix E may not contain any negative entries $e_{ij} = b_{ij} + r_{ij}$, the negative entries ($r_{ij} < 0$) of R must be compensated by entries $b_{ij} \geq |r_{ij}|$ of B. This is the mathematical fitting condition for R-matrices.

Furthermore, for stable EM all rows and columns of B and E must correspond to allowable valence schemes of the respective chemical elements. We call this the valence chemical boundary condition[9, 11].

Scheme 1



$$\begin{bmatrix} 0&1&0&0&0\\ 1&0&3&0&0\\ 0&3&2&0&0\\ 0&0&0&0&1\\ 0&0&0&1&6 \end{bmatrix} + \begin{bmatrix} 0&0&0&0&0\\ 0&0&0&0&0\\ 0&0&-2&1&0\\ 0&0&1&0&-1\\ 0&0&0&-1&2 \end{bmatrix} = \begin{bmatrix} 0&1&0&0&0\\ 1&0&3&0&0\\ 0&3&0&1&0\\ 0&0&1&0&0\\ 0&0&0&0&8 \end{bmatrix}$$

$$B(\mathbf{1}+\mathbf{2}) \quad + \quad R_1 \quad = \quad B'(\mathbf{3})$$

$$\begin{bmatrix} 0&1&0&0&0\\ 1&0&3&0&0\\ 0&3&0&1&0\\ 0&0&1&0&0\\ 0&0&0&0&8 \end{bmatrix} + \begin{bmatrix} 0&0&0&0&0\\ 0&0&-1&0&1\\ 0&-1&2&0&0\\ 0&0&0&0&0\\ 0&1&0&0&-2 \end{bmatrix} = \begin{bmatrix} 0&1&0&0&0\\ 1&0&2&0&1\\ 0&2&2&1&0\\ 0&0&1&0&0\\ 0&1&0&0&6 \end{bmatrix}$$

$$B'(\mathbf{3}) \quad + \quad R_2 \quad = \quad E(\mathbf{4})$$

Note that the R-matrix $R = R_1 + R_2$ converts **1** + **2** into **4**, and that R_1 must be used first; $B + R_2 = B'$ would violate the valence chemical boundary conditions.

A sequence of reactions or a reaction with a multistep mechanism is represented by an R-matrix $R = R_1 + R_2 + \ldots R_n$ whose components R_k correspond to the individual steps. The sequence of the transformations $B_k + R_k = B'_{k+1}$ is fixed by the mathematical fitting conditions and the valence chemical boundary conditions. Thus we have partially noncommuting addition[9].

Since any n × n matrices can be mapped onto points, or vectors in R^{n^2}, an n^2 dimensional euclidean space, we may «visualize» an FIEM of a collection **A** of n atoms as a lattice of points in R^{n^2} belonging to the distinct EM(**A**). A vector that leads from the BE-point P(**B**) to P(**E**) represents the reaction EM(**B**)→EM(**E**). The «city block distance» (distance in a space with L_1-metric) between the points P(**B**) and P(**E**) is called the chemical distance[8, 12, 14] between EM(**B**) and EM(**E**), because it corresponds to the number of valence electrons that are redistributed during the reaction EM(**B**)→EM(**E**). This topology of the FIEM is, in fact, a map of chemistry on which each and any conceivable chemical system has its well-defined place where it can be found, even if it belongs to unexplored territory.

The theory of the FIEM provides guidance within chemistry and is the foundation of many computer programs in chemistry that do not need a data base of detailed empirical chemical information[11]. Such programs have some almost «creative» capabilities.

4. The deductive Solution of chemical Problems and IGOR

The distinct categories of computer programs for the deductive solution of chemical problems correspond to the various types of solutions of the fundamental equation of our mathematical model of constitutional chemistry[11].

With a given BE-matrix B of an ensemble of molecules, EM(**B**), the solutions E of the equation $B + R = E$ represent those EM(**E**) which are interconvertible with EM(**B**) by chemical reactions or sequences thereof. This is precisely accomplished by the computer programs for the design of syntheses and the prediction of products that can be formed from given educts.

When the beginning, EM(**B**), and the end, EM(**E**), of a chemical reaction are known, the computer-assisted determination of the R-matrix that covers a minimal chemical distance between the EM corresponds to an atom-by-atom mapping of the educts onto the products of a reaction that achieves its result under the condition of minimal bond breaking/making[12]. A minimal chemical distance program can thus be used in the elucidation of reaction mechanisms, the optimization and evaluation of syntheses, and in the search for metabolic pathways[11].

When the R-matrix is given, the equation $B + R = E$ is solved by finding all pairs (B, E) that mathematically fit R under valence chemical boundary conditions. A computer program that accomplishes just this is capable of generating chemical reactions without precedence. The program IGOR (*I*nteractive *G*eneration of *O*rganic *R*eactions) is based on the above concept[15]. The BE-pairs (B,E) are generated through a stepwise procedure which begins with the first row/column pair of B and E. When the first row/column pair is found to agree with $b_{1j} + r_{1j} = e_{1j}$ under the mathematical fitting conditions and the valence chemical boundary conditions of the chemical element(s) chosen to belong to the first row/column pair of B and E, a compatible second row/column pair is determined, etc, until a full BE-pair is established. All other BE-pairs that obey the imposed conditions are found through this recursive procedure[15]. While the BE-pairs are being generated, they are subjected to a screening procedure, in order to eliminate forbidden substructures and to emphasize favored substructures.

In general, the number of BE-pairs that belong to a given R-matrix is immense. Note that with increasing complexity of the R-matrix the combinatorial multitude of BE-pairs decreases[15]. The number of BE-pairs that is combinatorially available for an n × n R-matrix has the upper bound

$$G(R) = \prod_{i=1,n} (5 - |r_{ii}|/2) \times \prod_{\substack{i=1,n-1\\ j=i+1,n}} (4 - |r_{ij}|)$$

For a typical 5 × 5 R-matrix we have $G(R) \approx 10^9$.

In order to be «creative», a computer program like IGOR must be able to take into account the set of all solutions and select some desirable subset of results without discarding too many solutions through arbitrary cut-off procedures. We avoid most of the combinatorial difficulties in IGOR and in our other recently developed computer programs for the deductive solution of chemical problems[11], by stepwise converging interactive procedures that follow a suitably established hierarchic classification of the prospective solutions, while the selecting decisions are preferably made by the user at critical levels of the hierarchy. The advantages of the aforementioned approach are illustrated by the bilateral design of syntheses[16], the program IGOR[15], the hierarchic documentation of chemical reactions[10], and a new, essentially exhaustive algorithm for the determination of the minimal chemical distance between isomeric EM[14, 17], including the corresponding atom-onto-atom mapping. Probably the most important advantage of the underlying convergent reduction of the problem-solving tree by stepwise hierarchic classification is the minimal use of ad hoc procedures and strategies, and the avoidance of heuristic rules which are often arbitrary and valid only in narrow areas, to prune divergent decision trees.

5. The Hierarchic Classification of Chemical Reactions

Until recently none of the attempts to develop a generally applicable and effective computer-oriented documentation system for chemical reactions has been very successful, because the traditional concepts do not afford an adequate classification of chemical reactions.

The DU-theory can be used to create hierarchic order in the set of all chemical reactions. This is not only well-suited as a basis of documentation systems for chemical reactions[10], but is also useful in the systematic computer-assisted discovery of new reactions[15].

In our approach chemical reactions are first classified according to the minimal number of valence electrons that must be redistributed in order to convert the educts into the products of the given reaction. This is accomplished by determination of the minimal chemical distance between the educts and products[12,14,17].

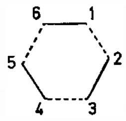
During a chemical reaction the redistribution of the valence electrons proceeds according to a distinct pattern which is characteristic of the given reaction. In the chemical literature this is represented by a pattern of «electron pushing arrows» which act on the educts. This redistribution can also be described by an R-matrix or its irreducible part, i.e. those rows/columns that contain non-zero entries. An irreducible R-matrix is obtained from a given R-matrix by deleting all zero rows/columns. The rows/columns of an irreducible R-matrix correspond to the reactive centers in the reactants, i.e. the atoms whose bonds or lone electrons participate in the reaction. These atoms form the «core of the reaction».

An irreducible R-matrix represents a category of reactions that have in common a characteristic electron redistribution pattern. An irreducible R-matrix[19] in canonical form is particularly suitable for documentation purposes. As early as in 1979 the representation of R-matrices by labelled graphs was used as a basis of computer programs for the classification of chemical reactions[20]. In the latter treatment the algebraic signs of the entries $r_{ij} = r_{ji}$ were used as labels of the edges in the graph, and the longest path with alternating labels was chosen to characterize the given R-matrix. This approach can serve to establish canonical R-matrices[10].

Note that if an irreducible R-matrix is convertible into a matrix with skew symmetry about the minor diagonal ($r_{ij} = r_{n+1-j,n+1-i}$) by row/column permutations, then it represents simultaneously both a reaction and its retro-reaction[15].

The irreducible R-matrix $R^c_{6,6}$ (the superscript «c» refers to an R-matrix with a cyclic electron flow pattern, whereas an «a» indicates an acyclic pattern)

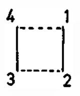
$$\begin{bmatrix} 0 & -1 & 0 & 0 & 0 & 1 \\ -1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & -1 & 0 & 0 \\ 0 & 0 & -1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & -1 \\ 1 & 0 & 0 & 0 & -1 & 0 \end{bmatrix}$$



describes the redistribution of electrons during many pericyclic reactions involving six electrons and six centers[11,19,21]. In fact, approximately 20% of 1900 investigated organic reactions belong to this category[22].

The most populated category of organic chemistry is represented by $R^c_{4,4}$

$$\begin{bmatrix} 0 & 1 & 0 & -1 \\ 1 & 0 & -1 & 0 \\ 0 & -1 & 0 & 1 \\ -1 & 0 & 1 & 0 \end{bmatrix}$$



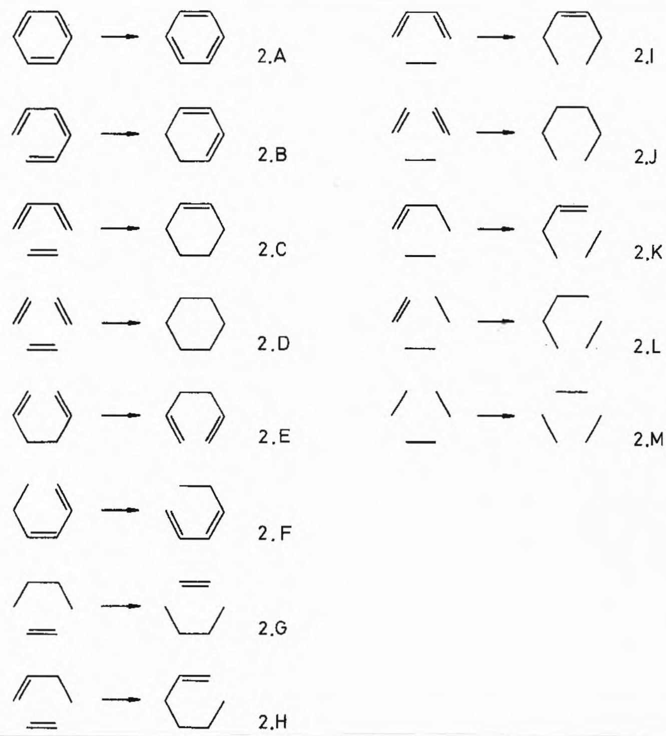
representing 50% of organic reactions.

The reaction categories can be further partitioned according to the «basis reactions» by specifying the bond orders of those bonds, which are affected by the reaction. These basis reactions often correspond to the so-called «reactions» and «name reactions» of organic chemistry, such as the Diels-Alder reaction, the Cope rearrangement, the ene-reaction, etc, as illustrated by Scheme 2.

When an electron redistribution according to ½ $R^c_{6,6}$ acts on Kekulé benzene, a «resonance form» **5e** is obtained. In the case of a concerted reaction the action of half an R-matrix leads to the representation of a transition state.

There are 20 distinct ways in which the «electron pushing arrows» of $R^c_{6,6}$ can carry out the automerization of Scheme 4 (see also Scheme 10).

Scheme 2



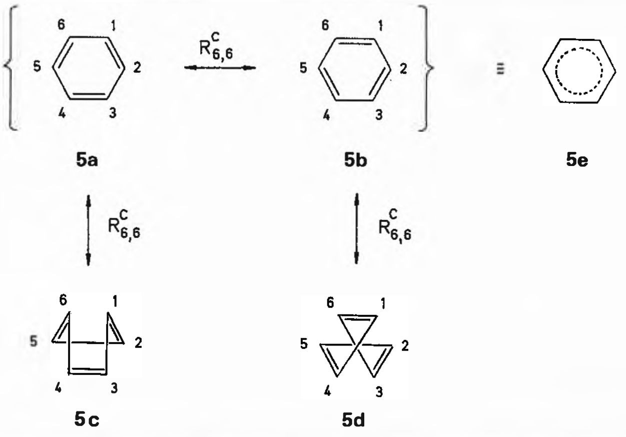
Note that an electron redistribution scheme does not always suffice to completely characterize a reaction, as has been observed through IGOR.

For example, resonance between **5a** and **5b** is represented by $R^c_{6,6}$; it involves three pairs of electrons. However, electron redistributions according to row/column permuted forms of $R^c_{6,6}$ lead also to **5c** and **5d**, though in this case through «automerization», however, according to a different basis reaction.

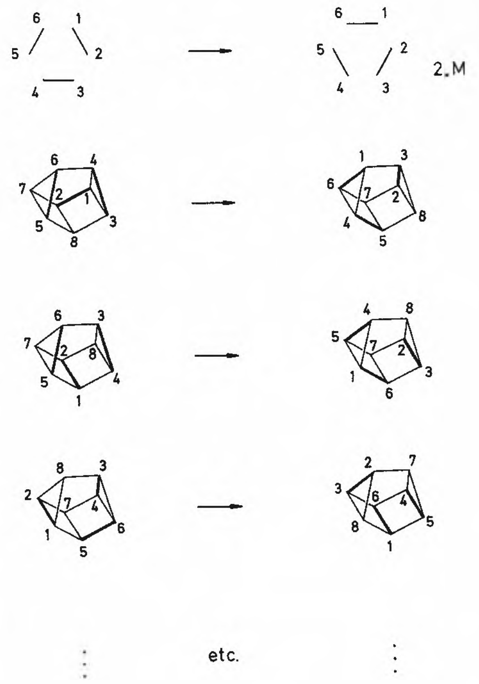
These examples indicate that the constitutional aspect of a chemical reaction is represented by $B + R = E$ only up to certain row/column permutations of the R-matrix. Redundancy and ambiguities are avoided only, if a row/column correlation is specified for all matrices in $B + R = E$. Recently a CANON[13] based algorithm has been incorporated into IGOR, an algorithm that recognizes the identity of chemical reactions unambiguously.

The steps that reduce an individual chemical reaction to its basis reaction are illustrated by Scheme 5.

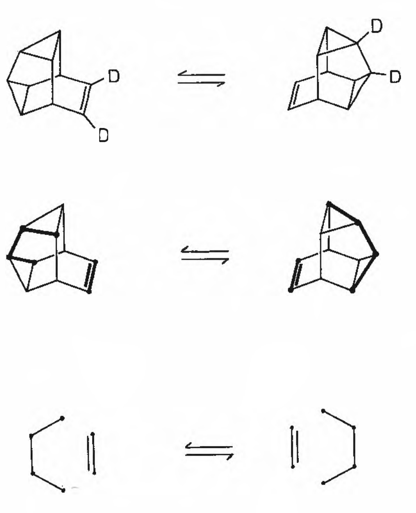
Scheme 3



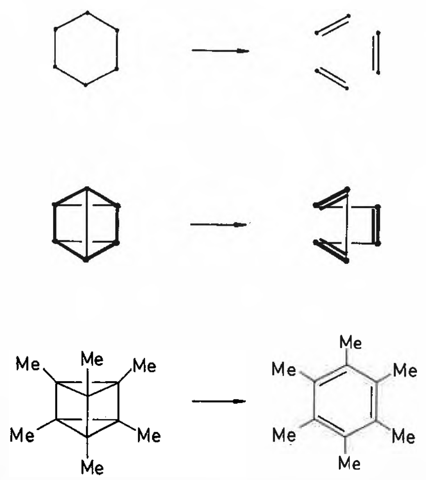
Scheme 4



Scheme 5



Scheme 6



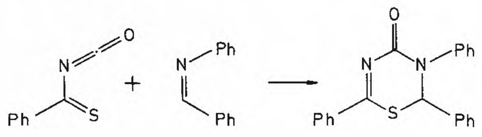
In Scheme 6 we find an example for the reverse process, the elaboration of an individual reaction from its basis reaction.

The basis reactions are further partitioned by specifying the chemical elements to which the reactive centers at the core belong. Thus the reaction of Scheme 7 defines a subset of the Diels-Alder reaction (see also Scheme 2).

Scheme 7

Finally, we successively reach the individual reactions by indicating the bonds and atoms outside the core of the reaction, e.g. for the hetero-Diels-Alder reaction[23] of Scheme 8.

Scheme 8



This hierarchic classification of reactions is indispensable for computer-assisted discovery of reactions by IGOR. While IGOR proceeds «down the hierarchy» from reaction categories towards individual reactions, the user directs IGOR at each level of the hierarchy in an active dialog in which the logical operations are performed by the computer according to the algorithms of IGOR, whereas the decisions that require a chemist's intuition and experience are left to the user.

Note that in the documentation of chemical reactions[10] the retrieval of reactions also proceeds «downwards»; the individual reactions are hierarchically ordered and stored «up the hierarchy».

6. New Reactions and their Degree of Novelty

Unprecedented chemical reactions may differ in degree of novelty. A reaction may be entirely new in all aspects, or it may be unprecedented but still a fairly close analogue of some known reaction. The relative novelty can be determined within the framework of the hierarchic order of chemical reactions.

A new reaction may be the first representative of a hitherto unknown category of reactions with a pattern of electron redistribution that has never before been encountered. Since there are approximately 100 conceivable categories of reactions[15], whereas only 45 of these contain known reactions[22], there remains some virgin territory consisting of more than 50 categories that are devoid of known reactions. On the other hand, a new reaction may belong to a known category of reactions but may still represent an unprecedented basis reaction.

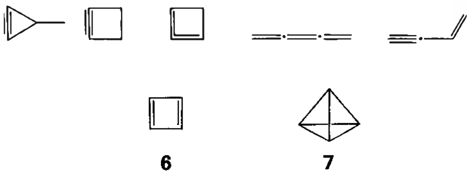
Least novel are those new reactions that belong to a known basis reaction but differ from other members of the basis reaction by the chemical elements at the core of the reaction, by external bonds of the core atoms, or by the periphery of the core[10].

7. Isomers and Isomerizations from IGOR

When the zero matrix is used as the input R-matrix of IGOR, it (or he?) generates the pairs (B,E) that are compatible with $R = 0$, i.e. it generates molecular structures given by $B = E$. Accordingly, the constitutional formulas of isomeric molecules can be obtained by IGOR when an empirical formula is combined with a zero R-matrix. Even with relatively few atoms the number of conceivable constitutional isomers is immense. Therefore, it is generally necessary to confine the output to subsets of isomers.

With C_4H_4 it is still possible to generate the whole family of isomers. When $(CH)_4$ is specified, only cyclobutadiene (**6**) and tetrahedrane (**7**), a subset of Scheme 9, appear[15].

Scheme 9



With C_8H_8 the family of constitutional isomers is already too large to be printed out and read by the user. When restricted to $(CH)_8$, we obtain the subfamily of the cyclooctatetraene valence isomers (Scheme 10)[15].

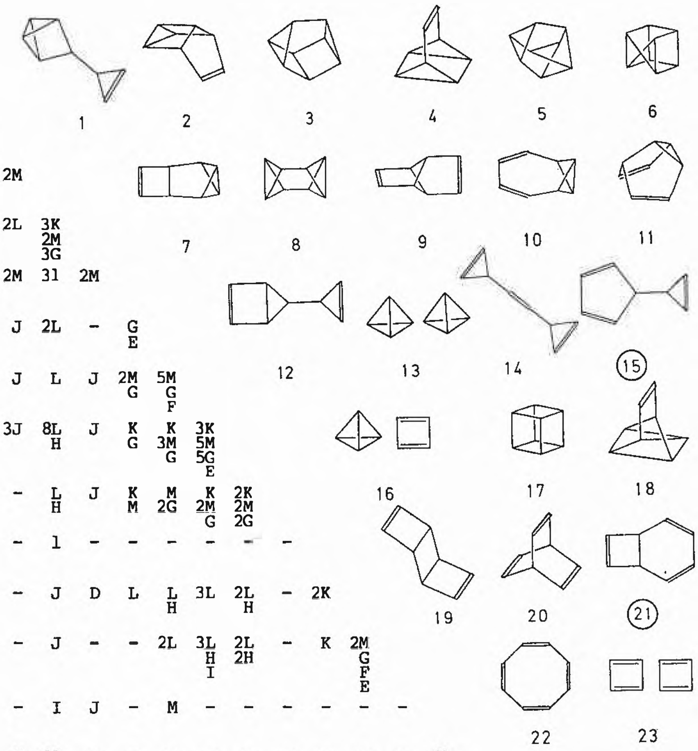
The conceivable valence isomerizations by $R_{6,6}^{c}$ within the $(CH)_8$ family can be obtained with IGOR by specifying reaction mechanisms in terms of their irreducible R-matrices or their basis reactions and by restricting the educt and the product to the $(CH)_8$ family. Scheme 11 shows, as an example, how ⑮ is converted into ㉑ by basis reactions.

The interconversions of these $(CH)_8$ valence isomers can occur according to the various basis reactions of Scheme 2.

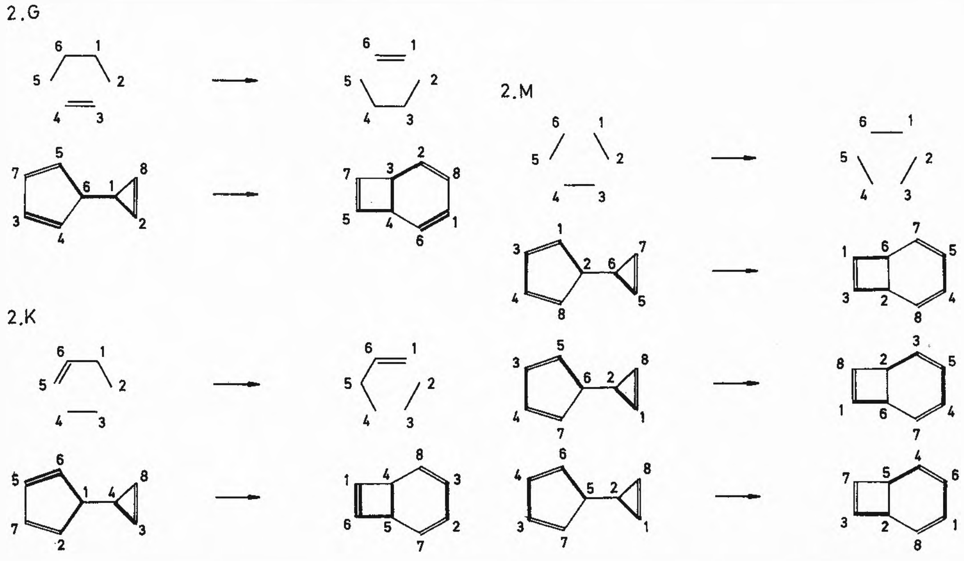
In Scheme 10 the entries at the intersections of the rows and columns belonging to the individual valence isomers are

Scheme 10

1	2K M G																						
2	4M 2G	3K 14M 9G																					
3	51	161	20M																				
4	M G	K 6M 2G	6L	K 5M 2G																			
5	1	51	5M	41	4M																		
6	-	31	6M	41	M	2M																	
7	M G	2K 5M G	6L	K 4M 2G	L	2L	3K 2M 3G																
8	1	31	4M	31	2M	2M	31	2M															
9	L	2L H	2J	3L	J	J	2L	-	G E														
10	L	4L I	4J	L H I	J	J	L	J	2M G	5M G F													
11	4L	10L 3H	6J	4L H	2J	3J	8L H	J	K G	K 3M G	3K 5M 5G E												
12	2L H	5L H	3J	4L	J	-	L H	J	K M	M 2G	K 2M G	2K 2M 2G											
13	-	-	-	-	-	-	1	-	-	-	-	-	-										
14	-	J	D	2J	-	-	J	D	L	L H	3L	2L H	-	2K									
15	3J	4J C	2D	2J	-	-	J	-	-	2L	3L H I	2L 2H	-	K	2M G F E								
16	-	-	-	-	-	-	I	J	-	M	-	-	-	-	-	-							
17	-	1	M	21	M	M	21	-	-	-	-	-	-	-	-	-	M						
18	-	K 3M G	3L	K G	L	2L	3M 2G	-	1	21	31	21	-	-	-	-	L	2M 2G					
19	L	6L H	J	L	J	2J	2L H	J	M	2M 2G	3K 2M G	K	-	1	1	G	J	2L H	2K M 4G E				
20	-	J	D	-	-	-	J	-	L	L	L H	L	-	-	K	-	D	-	3L H	-			
21	J	7J	D	3J C	D	D	3J	-	2L H I	3L 2H	4L 2H I	2L H	-	K	K 3M G	L	D	3J C	4L 2H	K	4K 7M 5G F E		
22	-	D	-	D	-	-	D	-	J	-	J C	J	-	I	L	-	-	D	J	I	3L B	3M	
23	-	-	-	-	-	-	D	-	-	J	-	-	-	-	-	-	-	-	C	-	L I	M	-
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23



Scheme 11

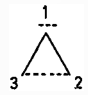


the indices of the basis reactions listed in Scheme 2. If an entry of the $(CH)_8$ valence isomerization table is a capital letter, the reaction proceeds from a «row» isomer to a «column» isomer, whereas a small letter refers to a valence isomerization of a «column» isomer into a «row» isomer. The reactions of Scheme 11 for instance, are given by the letters «G», «K» and «M» at the intersection of the row that belongs to ㉑, and the column of ⑮. A number in front of a letter indicates the multiplicity of ways a given basis reaction can act on the educt.

8. The Reaction Categories and Basis Reactions of Electrocyclic Reactions

The R-matrix $R^c_{4,3}$ involves four electrons and three reactive centers

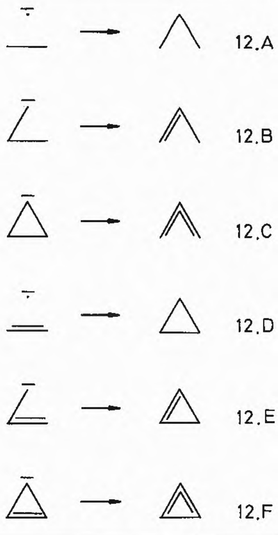
$$\begin{bmatrix} -2 & 1 & 1 \\ 1 & 0 & -1 \\ 1 & -1 & 0 \end{bmatrix}$$



and represents reactions having transition states with the topology of the π-system belonging to the cyclopropenyl anion. In the above graphs the dotted lines indicate the bonds and lone electron pairs that are removed by the reaction, whereas the full lines show where they are added.

IGOR generates from $R^c_{4,3}$ a set of basis reactions which cover practically all of the known chemistry of carbenes and nitrenes (see Scheme 12)[24].

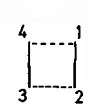
Scheme 12



Note that reaction 12.F can be eliminated by a substructure screening procedure.

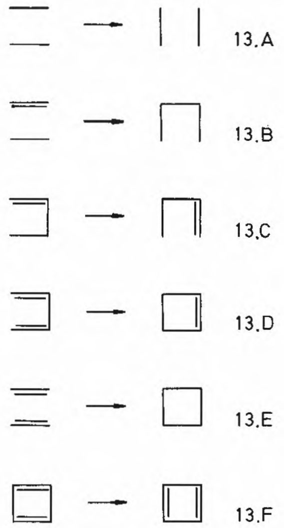
The electrocyclic reactions involving four electrons and four reactive centers are represented by the R-matrix $R^c_{4,4}$. The reactions of this category are represented by $R^c_{4,4}$ with the indicated «topology».

$$\begin{bmatrix} 0 & -1 & 0 & 1 \\ -1 & 0 & 1 & 0 \\ 0 & 1 & 0 & -1 \\ 1 & 0 & -1 & 0 \end{bmatrix}$$



According to IGOR, the corresponding category of reactions contains basis reactions of Scheme 13. With C-atoms at the reactive centers, they all represent known reactions.

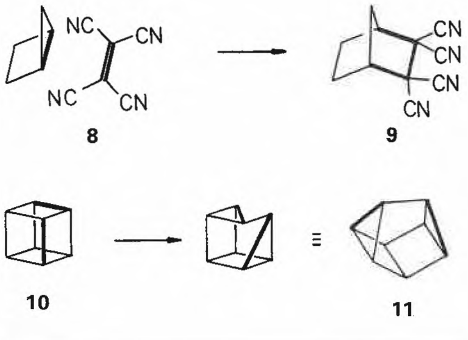
Scheme 13



Such reactions proceed via a cyclobutadiene-like antiaromatic transition state[5]; accordingly, they are photochemically allowed and thermally forbidden.

The ($\sigma_2 + \pi_2$)-cycloadditions proceed only with highly strained cyclic reactants[25]. The ($\sigma_2 + \sigma_2$)-cycloaddition also requires strain as the driving force, e.g. as is the case for the valence isomerization of cubane **10** into cuneane **11**[26].

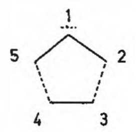
Scheme 14



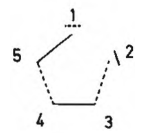
There exist three irreducible pentacentric R-matrices $R_{6,5}$ ($R^{c}_{6,5}$, $R^{c}_{6,5} = - R^{c}_{6,5}$, and $R^{a}_{6,5}$) that affect six electrons and five reactive centers; the corresponding reactions have a cyclopentadiene-like transition state and are thermally allowed (scheme 15).

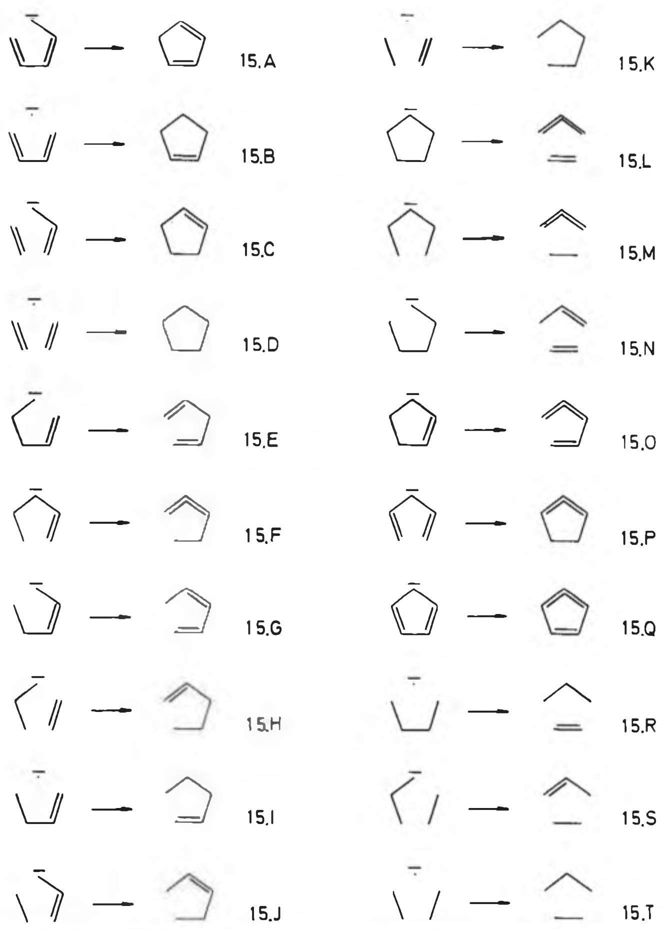
Scheme 15

$$R^{c}_{6,5} = \begin{bmatrix} -2 & 1 & 0 & 0 & 1 \\ 1 & 0 & -1 & 0 & 0 \\ 0 & -1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & -1 \\ 1 & 0 & 0 & -1 & 0 \end{bmatrix}$$



$$R^{a}_{6,5} = \begin{bmatrix} -2 & 0 & 0 & 0 & 1 \\ 0 & 2 & -1 & 0 & 0 \\ 0 & -1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & -1 \\ 1 & 0 & 0 & -1 & 0 \end{bmatrix}$$





A basis reaction of $R^{a}_{6,5}$ and 15.C corresponds to the original definition of 1,3-dipolar cycloadditions[27]. A recently improved definition requires electron octets for the 1,3-dipoles[28]. The corresponding basis reactions are generated from $R^{c}_{6,5}$.

When an element vector

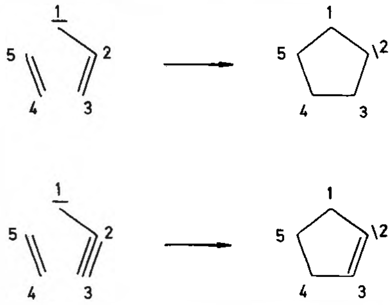
$$(1, 2, 3, 4, 5) = \begin{bmatrix} C & C & C & & \\ N & N & N & * & * \\ O & O & O & & \end{bmatrix}$$

is admitted, the 1,3-dipoles in octet form result (see Scheme 17) for the basis reaction of Scheme 16.

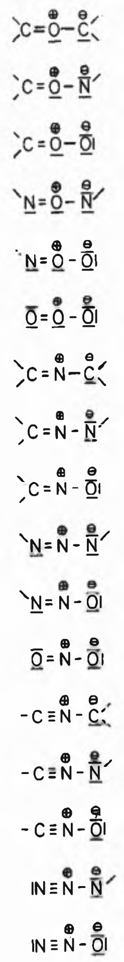
These 1,3-dipoles are all known[27,28] and, with two exceptions, they have been successfully subjected to (2 + 3)-cycloaddition.

The pericyclic reactions with six participating electrons and six reactive centers according to $R^{c}_{6,6}$ and a cyclic pattern of three «electron pushing arrows» are a reference system for the pericyclic reactions, comparable to benzene among the aromatic compounds.

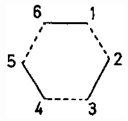
Scheme 16



Scheme 17



$$\begin{bmatrix} 0 & -1 & 0 & 0 & 0 & 1 \\ -1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & -1 & 0 & 0 \\ 0 & 0 & -1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & -1 \\ 1 & 0 & 0 & 0 & -1 & 0 \end{bmatrix}$$



Most $R^c_{6,6}$-reactions proceed in a concerted manner via an aromatic transition state[29]. *Mathieu* and *Valls* compiled 400 such reactions in a review article entitled «Le transfer electronique circulaire dans l'interpretation de certaines reactions de la chimie organique»[30]. *Hendrickson*[31] later found some further 79 $R^c_{6,6}$-reactions. Scheme 2 contains their basis reactions.

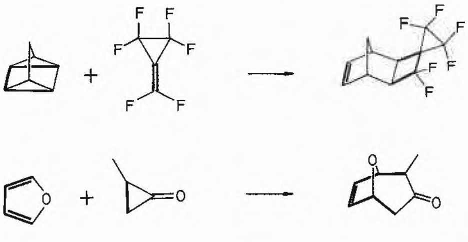
The basis reactions 2.B – 2.F belong to the well-known pericyclic reactions[5]. With decreasing π-participation, we have fewer known examples with C-atoms as the reactive centers, because a shift of π-bonds is easier to accomplish than breaking a C—C σ-bond. With few exceptions, from 2.G on, the only reactions that are known have atomic vectors with hetero atoms.

9. Search for New Reactions of the ene/retro-ene Type

Since the synthesis and modification of carbon skeletons is of particular interest, we first devoted our attention to the basis reactions of $R^c_{6,6}$ with C-atoms as the reactive centers.

Besides the well-known reactions of 2.B–2.F (Scheme 2) there are only a few examples for 2.G and 2.I with C-atoms at the core of the reaction (Scheme 18)[32,33].

Scheme 18



Since 2.J, 2.L, and 2.M are termolecular, and two C—C bonds are simultaneously broken in 2.K, 2.H remains the only one with a reasonable chance of realization.

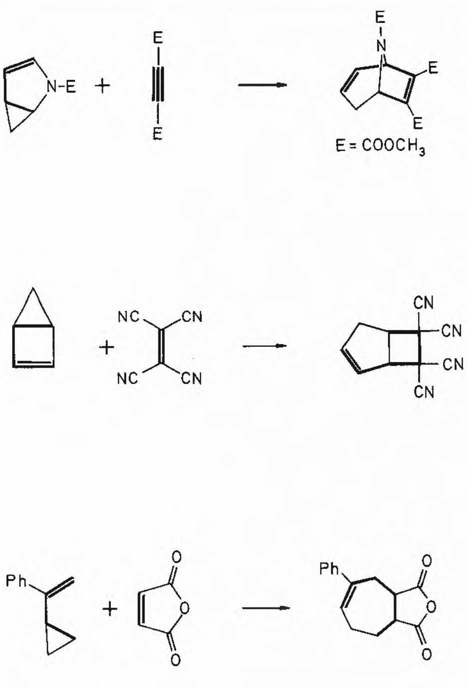
In Woodward-Hoffmann parlance the basis reaction 2.H is a $(\sigma_2\pi_2 + \pi_2)$-cycloaddition[5]. The best-known representative of this basis reaction is the ene-reaction[34] (Scheme 19), a 2.H-reaction with an atomic vector (H,C,C,C,C/O/N,C/O/N).

Scheme 19

Electron-poor olefins or carbonyl compounds serve well as ene-philes in the ene-reaction. The breaking/making of C—H-bonds and H-transfer is presumably the critical part of the ene-reaction. Since an analogous C—C-process is expected to be less likely, the critical breaking of a C—C-σ-bond must be facilitated. Incorporation in a three-membered ring and an adjacent hetero atom, or unsaturated group seems to be helpful. In fact, the only heuristic rules that have not been eliminated from our computer programs for the deductive solution of chemical problems[11] are such rules on preferential bond breaking/making. Another measure to enhance the likelihood of a 2.H-C_6 analogue of the ene-reaction is to enforce a favourable geometric arrangement of the reactive centers by incorporation into a suitable ring system[35].

None of the review articles or monographs contains any example of a 2.H-C_6-reaction. However, after our experimental realization of some new 2.H-C_6-reactions, a very thorough and systematic literature search led to the discovery of three published reactions of the 2.H-C_6 type[36]. All three had some of the aforementioned favourable features.

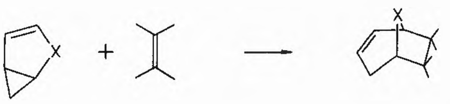
Scheme 20



Several authors could not repeat the last-mentioned reaction, even when using more reactive dienophiles[36].

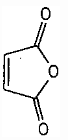
Thus the IGOR-assisted study of the 2.H-C_6-reaction leads to the system of Scheme 21 as the preferred candidates.

Scheme 21

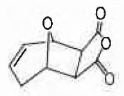


12

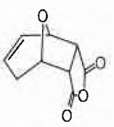
Homofurane (**12**, X = O) does indeed react with maleic anhydride (**13**) to form a 1:1 stereoisomer mixture of the expected product (**14**)[37].



13



14a

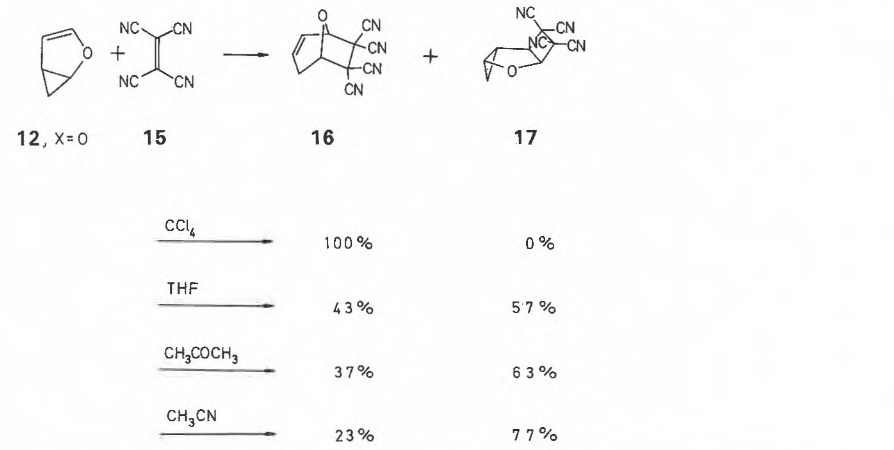


14b

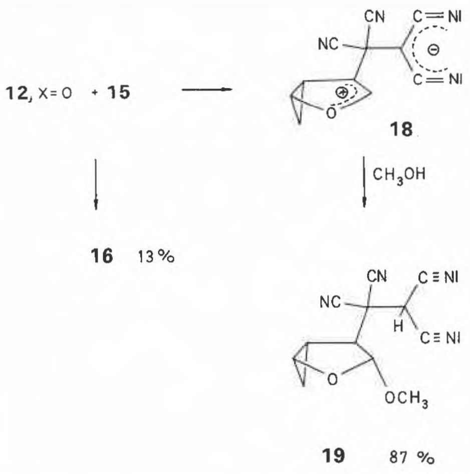
The reaction of homofurane with TCNE (**15**) leads at 24 °C to the formation of the (4 + 2)-adduct **16** as well as the (2 + 2)-adduct **17**, depending on the solvent (see Scheme 22).

In contrast to the (4 + 2)-cycloadditions, the concerted thermal $(\pi_2 s + \pi_2 s)$-reactions violate the orbital symmetry rules[5]: they ought to proceed via polar or radical intermediates. The expected zwitterion intermediate can be quenched by methanol[38]; at 20 °C in methanol 13% (4 + 2)-cycloaddition takes place, while 87% of the reactants form the zwitterion which adds methanol to form **19** (Scheme 23).

Scheme 22



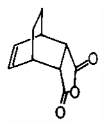
Scheme 23



The (2 + 2)-addition of TCNE to homofurane is reversible, whereas the (4 + 2)-reaction is not. In polar solvents, when scavengers are absent, the (2 + 2)-adduct is quantitatively converted into the (4 + 2)-adduct ($t_{1/2}$ = 6d at 60 °C in CD_3CN)[37].

The behavior of homothiophene (**12**,X = S)[37] and of *N*-ethoxycarbonyl-homopyrrole (**12**,X = NCO_2Et)[39] towards maleic anhydride (**13**) and TCNE (**15**) is closely similar to that of homofurane. Bicyclo[3.1.0]hex-2-ene (**20**) does not react analogously; it reacts with TCNE and maleic anhydride to form barrelene derivatives (**21**)[40].

20

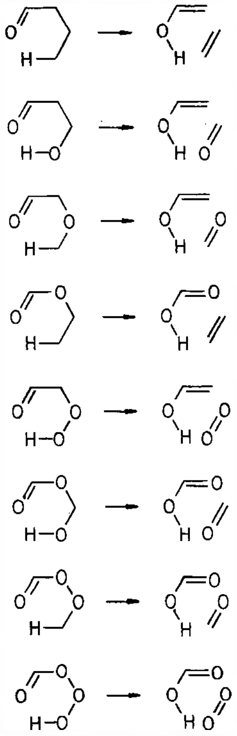


21

The retro-reaction of basis reaction 2.H is the extrusion reaction, the underlying pattern of the six-center pyrolytic eliminations.

The essential mechanistic features here are the transfer of a group «1» onto an sp^2 center «6» and cleavage of the bond «3–4», i.e. two single bonds are broken in the process. Therefore, no such reactions with C-atoms at all centers are known. With strategically placed hetero atoms at the reactive centers the likelihood of retro-2.H-reactions increases considerably. Thus with an element vector (1,2,3,4,5,6) = (H,C/O,C/O,C/O,C/O,O) the reactions of Scheme 24 are generated by IGOR.

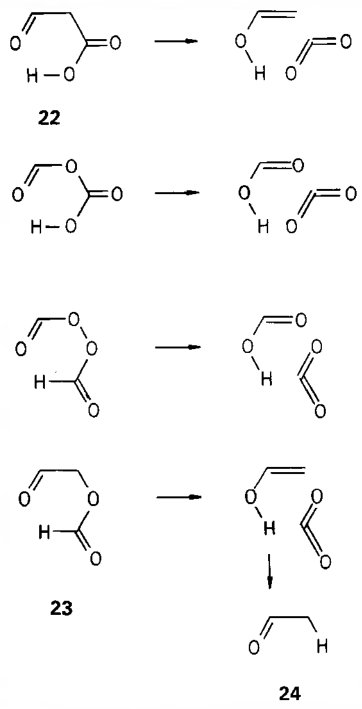
Scheme 24



Only one of these reactions, the pyrolysis of esters, is known; it proceeds at approximately 500 °C with an activation energy of approximately 180 kJ/mol[41]. None of the other above reactions seems likely or potentially useful for synthesis.

If the extrusion of CO_2, an energetically favoured species, is required as a further condition on such reactions, according to Scheme 25, their chances of occurrence improve considerably.

Scheme 25



The first of these reactions is the well-known decarboxylation of *β*-oxo carboxylic acids (**22**)[42]. The second seems to be possible, and an example is known for the third reaction[43]. But there is not much conceivable preparative use for the latter two. The fourth reaction of Scheme 25 is, however, unprecedented according to a careful search of the literature, and is potentially useful for synthesis. It could be employed for the synthesis of ketones (**24**) from the acyloins[44] via their formic acid esters (**23**). Such a process would be useful for the manufacture of the macrocyclic ketones – widely used in perfumery – from their readily available acyloins[45].

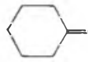
The pyrolysis of the *α*-formyloxy ketones (**23**), as «proposed» by IGOR, is best carried out in cyclohexane solution at 290 °C in an autoclave. 2-Butanone (**24a**,65%), desoxybenzoin (**24b**,48%), and cyclohexanone (**24c**,15%)

Et-CO-Me

24a

$Ph-CH_2-CO-Ph$

24b



24c

are thus obtained from the corresponding α-formyloxy ketones. The less than quantitative yields are presumably due to condensation reactions of the educts as well as the products.

Scheme 26 illustrates the dialog between the user and IGOR that led to the discovery of the latter new reaction. Note the guidance by the hierarchic classification of reactions.

10. Perspectives

The new reactions that have been recently found with the aid of IGOR are moderately novel by the standards of Section 6. As such they are probably not very important from a preparative point of view, but it is noteworthy that they were predicted by IGOR and then realized in the laboratory. The results obtained are not only an experimentum crucis for IGOR, but also signify that a powerful qualitative theory of chemistry, and the order which it reveals, can be combined with artificial intelligence methods to yield converging problem-solving computer programs that are capable of reaching new dimensions in chemistry.

By its particular design and its favourable assignment of the roles that man and machine have to assume in their interaction, a computer program like IGOR is capable of enhancing a chemist's creativity. Also, the use of such a computer program for the deductive solution of chemical problems teaches the user to approach organic chemistry in a more systematic fashion. Moreover, like many good teaching devices, IGOR is an enjoyable toy.

After some improvements have been implemented, it will soon become generally available as a tool for the systematic exploration of the remaining virgin territories of organic chemistry.

The future users of IGOR cannot expect instant success. According to our experience it takes half a year or more before a new user is able to use IGOR comfortably in a meaningful and productive manner. The most difficult part of learning to use IGOR is to acquire the capability of judging whether or not a newly generated chemistry is close to or far from realizable chemistry; in the remote areas of unexplored chemical space our customary analogist's reasoning provides little guidance.

One of the most important results of IGOR is the insight that known chemistry is still a very small subset of conceivable chemistry. The reaction category of Prileshaev epoxidation illustrates the vastness of chemical space (see Section 3); this category contains well over 10^4 unexplored basis reactions (see Section 6).

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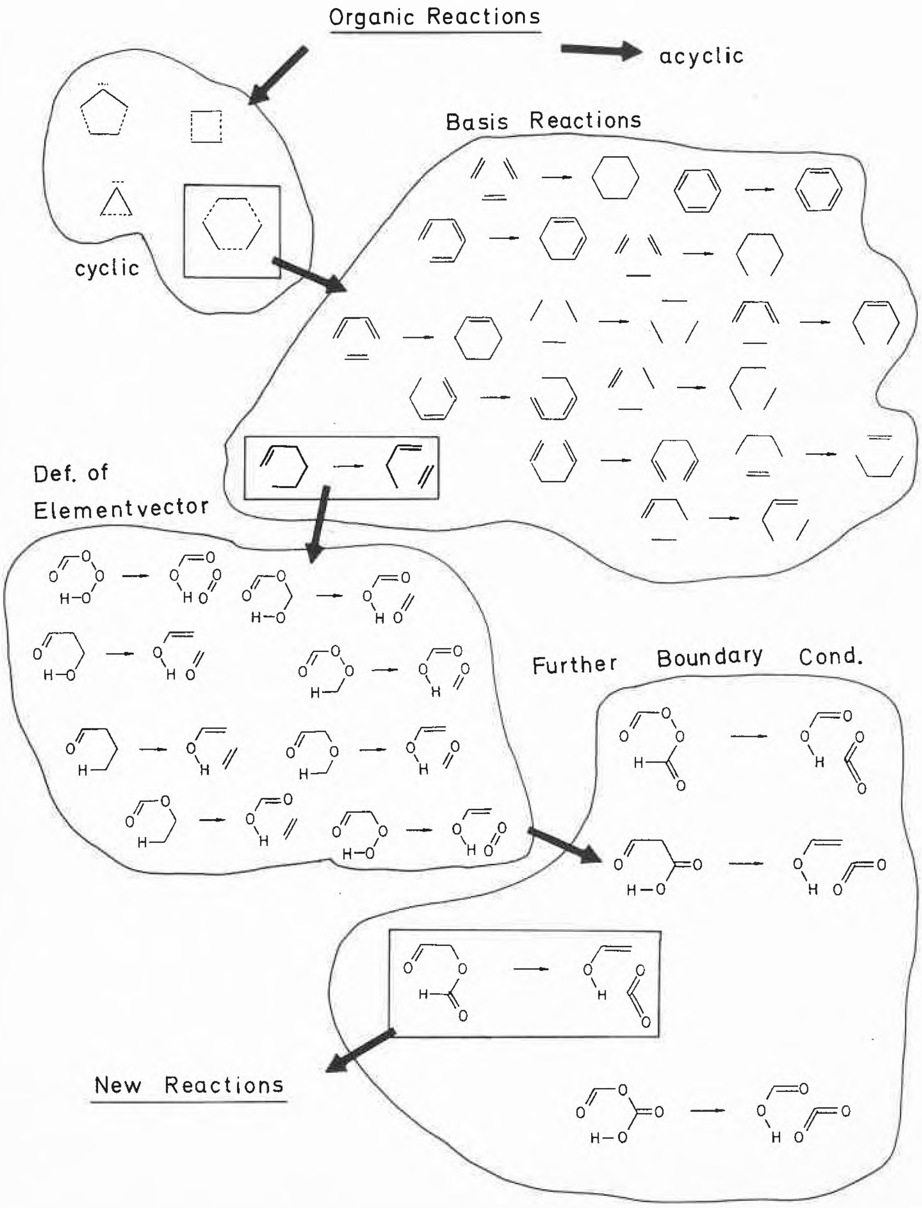
Scheme 26



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