

# Problems of Molecular Design and the Computer. 11. The FLAMINGOES Program System for the Nonempirical Solution of Structural Problems of Organic Chemistry. The BASIC Program Oriented for Microcomputer

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The general principles and structure of the nonempirical FLAMINGOES program system for the solution of synthetic and mechanistic problems of organic chemistry are described. The main fields of application of this multipurpose program are the following: synthesis planning; investigation of molecular rearrangements; and searches for the possible mechanisms of organic reactions. Some results obtained with the help of the FLAMINGOES program system are briefly presented.

## I. INTRODUCTION

The long history of organic synthesis has many significant achievements, but the area is still generally accepted as an art. Several features explain this situation, e.g., (i) the overwhelmingly large number of possible synthetic strategies to any planned targets, (ii) the combinatorial explosion of possible synthetic routes and variations in the frame of any given synthetic strategy, and (iii) the low predictive power of the theoretic concepts, which do not help to predict the yields of individual reactions or whether they will succeed or fail. The greatest challenge to this "state of the art" concept has been the creation of computer-assisted programs for the efficient and systematic planning of synthetic and structural problems of organic chemistry.

In spite of the short history of these computer-assisted planning methods, one can trace two branches in their development. A characteristic feature of the first category of synthesis design methods is that the well-known reactions are stored in a library of transformations. These methods are empirically oriented.<sup>1-5</sup> The second group includes mechanistic or logic-oriented nonempirical methods,<sup>6-10</sup> which are constructions of chemical process with purely combinatorial procedures. The potential advantage of this approach is that it may lead to an intelligent discovery of novel reactions in organic chemistry.

Since 1972 we have been developing a formal-logical approach to a solution of a variety of structural problems in organic chemistry.<sup>11-16</sup> One of the results of this development has been the multipurpose computer program system FLAMINGOES (Formal-Logical Approach to Molecular Interconversions, Nonempirical Generation, Orientation, and Evaluation of Syntheses).<sup>16</sup> Our approach to the structural problems of organic chemistry is nonempirical in essence, so FLAMINGOES is based on the logical-combinatorial construction of the formal reaction schemes.

The purpose of this paper is to consider the general principles and the strategy of the FLAMINGOES program system, which is written in BASIC and specially oriented to the microcomputer (64K). Additionally, we shall very briefly present the results of the exploitation of the FLAMINGOES program system.

## II. BASIC PRINCIPLES OF THE FORMAL-LOGICAL APPROACH AND CHEMICAL STATEMENT OF THE PROBLEM

The fundamentals of the formal-logical approach to organic reactions together with necessary terminology were previously described in detail.<sup>16</sup> In the present work we shall present only the basic principles of this approach.

A chemical system (CS) may consist of one or several substances with the structures given in a form of chemical graph. For the description of the reactions we take into account only the overall results of organic reactions, namely, the

structures of initial and final CS's. The mechanisms or sequential steps of the actual processes are ignored. The most important types of organic reactions can be described as a result of the cyclic bond redistributions (CBR's) in the initial CS leading to the final CS.<sup>16,17</sup>

First we choose the atoms for which the number or the disposition of bonds may be changed in the course of the possible chemical reactions in a given CS. These atoms will be referred to as potential reaction centers (PRC's).

Only a portion of the PRC's are involved in each CBR. We call them reaction centers (RC's). The number of RC's determines the size of the CBR. There are two different types of RC's for the processes with CBR: (1) ordinary RC's (ORC's) with the formal valency numbers that are unchanged in the course of CBR; (2) specific RC's (SRC's), which change their valency numbers by two units.<sup>11</sup> If one chooses the noncharged and nonradical resonance structures for the description of chemical reaction, any reaction with CBR can be described in terms of only these two types of RC's.<sup>11</sup>

Thus, it is necessary to select the PRC's for which changing of the valency is allowed. For this subset of potential SRC's (PSRC's) we choose the allowed valency changes from the following possibilities: (1) conservation and decrease of the valency; (2) decrease only; (3) conservation and increase; (4) increase only; (5) increase and decrease; (6) conservation, increase, and decrease. The PRC's that are not labeled as PSRC's will retain their valencies in any possible process with CBR.

Figure 1 illustrates the application of this approach to the description of reactions in three different CS's. This approach enables us to describe the linear transfers resulting in the charged or radical structures in a similar way. In this case one must include the so-called "phantom centers", namely, symbols +, -, and · (the sign for a radical) in the set of PRC's.<sup>16</sup>

The FLAMINGOES program system is based on the systematic nonduplicated generation of all possible cyclic bond redistributions in a given CS. This procedure makes it possible to obtain a set of all appropriate final CS's, representing reactions that correspond to CBR's thus generated.

If some results seem to be promising for further investigation, the procedure can be extended to construct the complete synthesis tree (i.e., of some graph with the vertices corresponding to initial, intermediate, and final CS's and the edges corresponding to the generated CBR's, which can be interpreted as the appropriate interconversions of these CS's).

## III. MATHEMATICAL STATEMENT OF THE PROBLEM<sup>18,19</sup>

Let  $G_{pq}$  be the indirected graph with the set of nodes  $V = \{v_i\}$ ,  $i = 1-p$  and the set of edges  $X = \{x_j\}$ ,  $j = 1-q$ . It is well-known that the sequence of nodes  $v_1, v_2, \dots, v_n, v_{n+1}$  forms

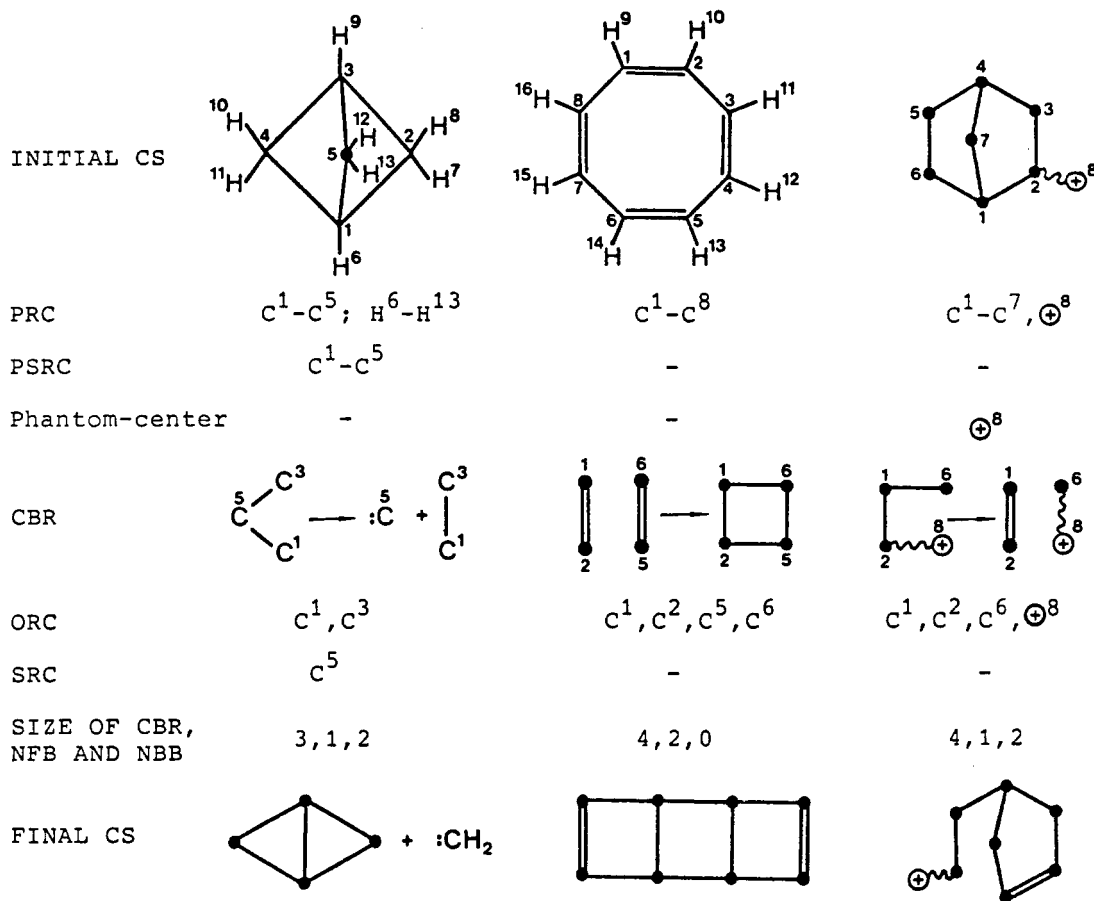


Figure 1. Application of the formal logical approach for description of organic reactions.

an ordinary cycle if (a)  $n \geq 3$ , (b)  $v_1 \equiv v_{n+1}$ , (c)  $v_i \neq v_{i'}, i, i' \leq n$ , and (d)  $v_i v_{i+1} \in X$ . Similarly, the sequence of nodes  $v_1, v_2, \dots, v_n, v_{n+1}$  will be said to form an  $n$ -pseudocycle  $\varphi$  if it satisfies only the conditions a-c. In this case the pair(s)  $v_i v_{i+1}$ ,  $i = 1-n$ , not belonging to  $X$  will be said to be pseudoedge(s). We believe all the edges (pseudoedges) of  $\varphi$  to be different from other edges (pseudoedges) of  $G_{pq}$ . The complete set of  $n$ -pseudocycles  $\Phi_n$  of any graph with  $p$  nodes evidently consists of  $|\Phi_n| = \frac{1}{2} C_p^n (n-1)!$  elements. Further, the node automorphism group  $\Gamma$  of the graph  $G_{pq}$  induces the other permutation group  $\Gamma^*$  of the power  $|\Phi_n|$ ; note that  $|\Gamma^*| \leq |\Gamma|$  and depends upon graph structure. The pseudocycle  $\varphi$  will be called equivalent to the pseudocycle  $\varphi'$  (with respect to the group  $\Gamma^*$ ) if it can be transformed to  $\varphi'$  by the action of any permutation  $\gamma^*$  belonging to  $\Gamma^*$ ; thus,  $\varphi \sim \varphi' \Leftrightarrow \exists \gamma^* \in \Gamma^*$  such that  $\gamma^* \varphi = \varphi'$ . It is well-known that any permutation group partitions the corresponding set into several pairwise disjoint subsets (equivalence classes or orbits), each consisting of equivalent elements. Hence, the set  $\Phi_n$  can be uniquely partitioned into the orbits of the group  $\Gamma^*$ . In order to consider only pseudocycles satisfying the given restrictions, the set  $P$  of predicates (or special conditions) must be introduced. All predicates of  $P$  must be determined for any element of  $\Phi_n$  and, moreover, invariant with respect to the action of the group  $\Gamma^*$ . The subset of  $\Phi_n$  consisting of those  $n$ -pseudocycles that satisfy all predicates forms the set  $\Phi_n^*$ ; thus,  $\Phi_n^* = \{\varphi \in \Phi_n : P(\varphi)\}$  and  $|\Phi_n^*| \leq |\Phi_n|$ .

It is clear that (i) the set  $\Phi_n$  of  $n$ -pseudocycles describes all  $\frac{1}{2} C_p^n (n-1)!$  possibilities for the attachment of  $p$  PRC's on  $n$  vertices of a regular polygon, (ii) the set  $\Phi_n^*$  corresponds to those attachments that satisfy the given chemical restrictions, and (iii) the group  $\Gamma^*$  determines the symmetry relations between such attachments (also called reaction systems<sup>16</sup>). Thus, the first combinatorial problem is how to generate an arbitrary system of representatives, each representing a single

orbit of the group  $\Gamma^*$  acting on  $\Phi_n^*$ .

Let us consider now the set  $D = \{d_i\}$ ,  $|D| = n$ , consisting of all edges and pseudoedges of a fixed  $n$ -pseudocycle  $\varphi$ . The function  $f$  from  $D$  to the set  $R = \{+1, -1\}$  will be viewed as the pseudocycle labeling. The complete set of such functions  $F = R^D = \{f : D \rightarrow R\}$  evidently consists of  $2^n$  elements. The node automorphism group  $\Gamma$  of the graph  $G_{pq}$  induces a certain permutation group  $H$ , acting on  $D$ . The order of this group depends on the structure of  $G_{pq}$  and on the choice of  $n$ -pseudocycle; it is clear that  $|H| \leq |\Gamma|$ . On the other hand,  $H$  is isomorphic with some subgroup of dihedral group; hence, the order of  $H$  is a factor of  $2n$ . Further, the group  $H$  induces the other permutation group  $H^*$  acting on the set  $F$ ; hence, the equivalency relation between pseudocycle labeling can be introduced:  $f \sim f' \Leftrightarrow \exists h^* \in H^*$  such that  $h^* f = f'$ . This means in turn that the set  $F$  can be uniquely partitioned into several pairwise disjoint subsets (equivalency classes or orbits of  $H^*$  on  $F$ ); each of these subsets evidently consists of the functions  $f$  being equivalent with respect to  $H^*$ . Similar to the set  $P$ , the set of predicates  $Q$  (reflecting the given restrictions) can be introduced. All predicates of  $Q$  must be determined for any element of  $F$  and, moreover, invariant with respect to the action of  $H^*$ . The subset of  $F$  consisting of those pseudocycle labelings that satisfy all predicates of  $Q$  forms the set  $F^*$ ; thus,  $F^* = \{f \in F : Q(f)\}$  and  $|F^*| \leq |F|$ .

It is easy to see that (i) the set  $F$  of  $n$ -pseudocycle labelings describes all  $2^n$  formally possible ways to change the orders for  $n$  chemical bonds being situated on the edges of a regular polygon, (ii) the set  $F^*$  corresponds to those ways that satisfy the given chemical restrictions, and (iii) the group  $H^*$  determines the symmetry relations between the possible ways of changing bond orders. As a result the second combinatorial problem arises: how to generate an arbitrary system of representatives, each representing a single orbit of the group  $H^*$  acting on the set  $F^*$ ?

The overall problem may be briefly formulated as follows: how to generate the complete set of nonequivalent (with respect to  $H^*$ ) labelings for all nonequivalent (with respect to  $\Gamma^*$ )  $n$ -pseudocycles (the values of  $n$  being given)? This problem has been shown to be correct, and the corresponding original algorithm has been elaborated.

#### IV. REJECTION OF CBR'S RESULTING IN THE UNREAL AND DUPLICATE CS'S: PRINCIPLE OF THE EARLIEST REJECTION

The systematic generation of CBR's is accomplished by means of an algorithm for the construction of nonequivalent graph edges rearrangement. The solution of such problems for graphs is based on lexicographic inspections of the so-called selection trees.<sup>20</sup> Such an inspection of the complete selection tree leads to both suitable and interesting results and also to a great number of unreal or duplicate CS's. Hence, it is necessary to include some selection criteria in order to reduce the selection tree for greater chemical and mathematical accuracy.

There are three selection criteria in the FLAMINGOES program system. First, the formal criterion consists of checking the correct atom valencies and bond orders. As was mentioned above, there are two different types of PRC's. Thus, any CBR resulting in a change of the valency of the ORC must be rejected. Similarly, the real change of the valency for any SRC must be in correspondence with one of the admitted variants (see part II).

The CBR's resulting in the break of the bond of zero order as well as the CBR's resulting in the increase of the bond order to four are also rejected by this criterion.

Second, the empirical criterion restricts the range of the search. In order to restrict the number of mathematically correct but chemically uninteresting decisions, the FLAMINGOES program is allowed to generate either all possible CBR's for a given CS or only those that are controlled by the given size, the number of SRC's, and the number of forming (NFB) and breaking (NBB) bonds. The chemist can introduce these limitations in the dialogue, according to his or her own chemical knowledge and experience. CBR's not satisfying the given restrictions are rejected by this criterion.

It should be mentioned that the admitted NFB's and NBB's are in correspondence with the types of admitted reactions in a given CS. The general types of reactions with CBR were described elsewhere.<sup>12,13</sup> Two characterizing numbers exist for each of these types, namely, the NFB and NBB. For example, for the sigmatropic rearrangement NFB = 1 and NBB = 1 because in the course of this reaction one  $\sigma$ -bond is broken and one  $\sigma$ -bond is formed. Similarly, for the  $[2 + 2]$ -cycloaddition NFB = 2 and NBB = 0. For the opposite reaction, i.e., for cyclofragmentation NFB = 0 and NBB = 2.

Third is the equivalency criterion. The generation of CBR's in a CS possessing several equivalent structural elements necessarily produces duplicates. This criterion avoids such duplications at the stage of the CBR construction; it is based on the information about the automorphism group of the graph, corresponding to the initial CS (vide infra).

The different criteria act at different stages of search. Evidently, the early rejection of unsatisfactory results means an increase of program efficiency (the principle of earliest rejection). In the FLAMINGOES program system the most important criteria operate at the stage of CBR construction, long before the generation of the final CS.

#### V. THE FLAMINGOES PROGRAM SYSTEM

The present version of FLAMINGOES is specially adapted for organic chemists; it is written in BASIC for microcomputer

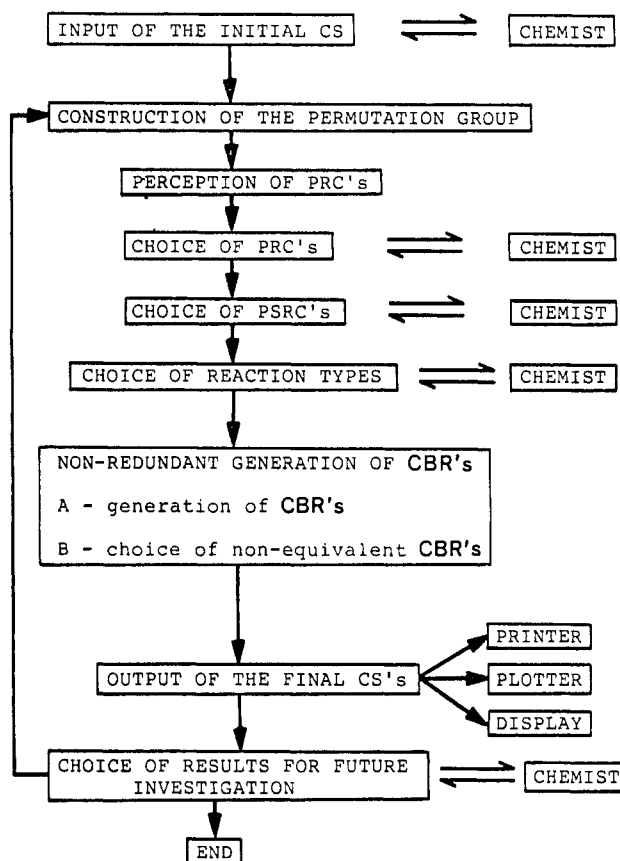


Figure 2.

Iskra-226.6 (64 K). The chemist can easily employ this flexible program interactively due to the graphical interface. The user's restrictions on CBR generation (see part IV) are accepted as keyboard input. Substantial efforts were made to increase the speed of the main combinatorial subroutine, so that this large program could be adapted to a microcomputer. The average time for the generation of a single final CS requires 3–5 s. The present version of FLAMINGOES includes nine main subroutines and is stored in 60 KB of computer memory. The general structure of the program is depicted in Figure 2.

(1) **Input of the Initial CS.** During this procedure a chemist inputs the drawing of the initial CS in the graphical display. The CS is then represented within the program by an adjacency matrix of the multigraph describing the structure of initial CS. The chemist also inputs the number of stages of synthesis (up to six).

(2) **Construction of Permutation Group.** This subroutine automatically generates all permutations of the automorphism group of the graph corresponding the initial CS. This information is necessary to obtain the nonequivalent CBR's in the generation subroutine and for the realization of the equivalency criterion (see part IV). This subroutine employs the BASIC version of the FORTRAN program AUTOGRAPH, which is based on the original mathematical procedure of the permutation group generation.<sup>21</sup>

(3) **Perception of PRC's.** Among the centers of the given CS, the program perceives the PRC's, namely, the centers representing heteroatoms, centers adjacent to heteroatoms, and atoms linked by multiple bonds. For the future development of the FLAMINGOES program system we are planning to supplement the subroutine by recognizing small strained carbon rings and allylic systems in the molecule.

(4) **Choice of PRC's.** During this subroutine a chemist may arbitrarily correct the set of PRC's proposed by the program. It is possible to include/exclude any centers of CS of this initial set.

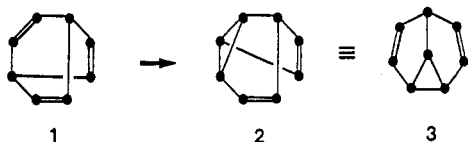


Figure 3.

(5) **Choice of PSRC's.** During this subroutine the chemist chooses the centers, which may change their valency numbers, out of the set of PRC's. For each of the chosen PSRC's the chemist must also point out the admitted variant of the valency change. This information is necessary for the realization of formal criterion (see part IV).

(6) **Choice of Reaction Types.** During this subroutine the chemist inputs some limitations on the following: sizes of CBR's, numbers of SRC's, NFB, NBB. This information is necessary for the realization of empirical criterion (see part IV).

(7) **Nonduplicate Generation of CBR's.** This is the main combinatorial subroutine in the FLAMINGOES program system. The execution time of this subroutine determines the response time of the system. Module A performs the lexicographic inspection of the selection tree and generates possible CBR's. The formal and empirical criteria are implemented in this procedure. Module B implements the symmetry criterion on the basis of the permutation group obtained in the subroutine 2. Thus, only those CBR's are generated that represent nonequivalent pseudocycle labelings concerning the action of the groups  $\Gamma$  and  $H$  (see part III).

(8) **Output of the Final CS's.** It is possible to output the structure of the final CS on the printer (in the form of linear code for CBR) or on a graphical display and plotter (in the form of drawings). It should be noted that the initial coordinates of centers of initial CS remain constant during the output of result, and, hence, the final CS may be represented in an unusual way. For example, the transformation of Figure 3 will be depicted as 1 to 2, not as 1 to 3.

(9) **Selection of Results for Further Investigation.** The chemist may choose the final CS's that appear to be interesting for further investigation from the set of results obtained at the last stage of search. These CS's are stored in a special data file within the program; the maximum number of results accumulated in the  $i$ th stage for investigation at the  $(i + 1)$ th stage is 16. After the exhaustive generation of all CBR's for initial CS, the program takes from this file the recorded results and introduces them as initial CS's for the next stage of search. Thus, the synthesis tree is developed in a breadth-first manner<sup>22</sup> up to the sixth level.

## VI. APPLICATION OF THE FLAMINGOES PROGRAM SYSTEM FOR THE SOLUTION OF SYNTHETIC AND MECHANISTIC PROBLEMS IN ORGANIC CHEMISTRY

To demonstrate the possibilities of the FLAMINGOES program system we briefly describe here the computer search and the investigation of (i) the synthetic pathways of some cage structures, (ii) the various rearrangements in the isomer's families, and (iii) the possible mechanisms of the organic reactions (including the ionic and radical intermediates). The results, generated during this computer search, are of undoubted interest, and some of them are very promising for practical realization. A detailed description of the results for each of the problems considered will be published separately.<sup>23</sup> In this paper we shall mention only general characteristics of these results (Figures 4–6).

The main results were (1) reproduction of all published synthetic approaches, (2) generation of a series of promising new pathways to the target structures, and (3) selection of some particular reaction types leading to the target structures.

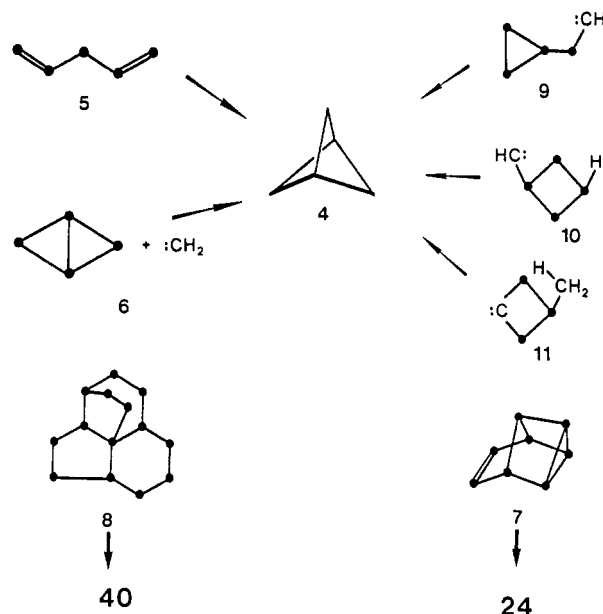


Figure 4. Number of strategic synthetic pathways.

Using the simplest example of bicyclo[1.1.1]pentane, Figure 4 demonstrates (1) reproduction of all known pathways (transformations  $5 \rightarrow 4^{24}$  and  $6 \rightarrow 4^{25}$ ; please take into consideration that the pathway  $5 \rightarrow 4$  is not trivial and is not self-evident); (2) selection of the definite type of reactions, for instance, the intramolecular insertion of carbene (in this case four possible strategic synthetic pathways,  $6 \rightarrow 4$ ,  $9 \rightarrow 4$ ,  $10 \rightarrow 4$  and  $11 \rightarrow 4$ , were suggested). Some of the suggested pathways are promising.

Many synthetic pathways worthy to be analyzed were proposed for tetracyclo[3.3.0.0<sup>2,4</sup>.0<sup>3,6</sup>]oct-7-ene (7) and the carbocyclic skeleton of ( $\pm$ )-quadron (8); Figure 4 shows the number of potential strategic pathways generated by the FLAMINGOES program.

Many new interesting possibilities revealed with FLAMINGOES have been found in the course of the investigation of the interconversions (for instance, proceeding as the cycloadditions, sigmatropic rearrangements, and electrocyclic reactions) among the isomers of the cyclopolyene families  $(CH)_n$  ( $n = 4, 6, 8, 10$ ). For  $(CH)_n$  isomers ( $n = 8, 10$ ), along with the known rearrangements, the FLAMINGOES program system predicted a large number of potentially possible rearrangement processes, including new pathways to  $(CH)_8$  and  $(CH)_{10}$  families.

Another application of the FLAMINGOES program is the computer investigation of the rearrangement pathways. As an example, the search for all cationic structures capable of being rearranged into 2-norbornyl cation during a one- or two-stage process was carried out (Figure 5). The FLAMINGOES program system generated 12 one-stage and 71 two-stage routes to 2-norbornyl cation as well as 39 various cationic structures which, in principle, are capable of rearranging into this cation. The so-called " $\pi$  route" (Figure 5) generated by the program at the first stage (transformation  $13 \rightarrow 12$  is a well-known process,<sup>26</sup> but very promising "double- $\pi$  routes" (Figure 5), proposed at the second stage of computer search, seem to be not yet investigated.<sup>27</sup>

According to the experimental data, the treatment of 2-vinyl-1,1-bis(bromomethyl)cyclopropane (14) with different reducing agents gave only a small yield of the expected vinylspiropentane (15), but eight other hydrocarbons (16–23) were isolated (Figure 6).<sup>28</sup> The computer investigation of this reaction included the generation of the "tree" of the possible intermediates and their interconversions. The productivity of the program can be demonstrated by the following numbers:

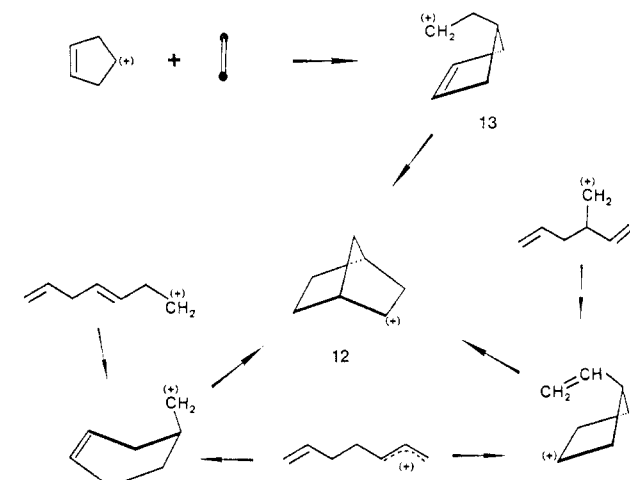


Figure 5.

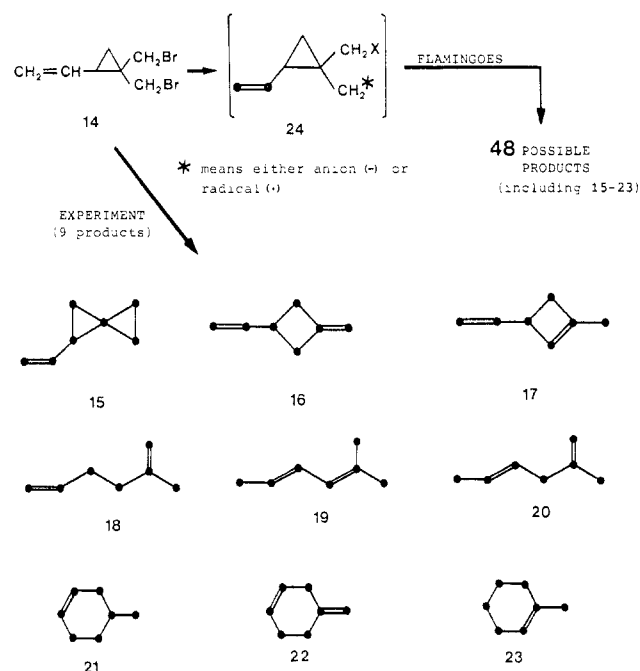


Figure 6.

30 possible intermediates for this reaction as well as 90 possible ways of transforming the intermediate (24) and 48 possible products were revealed. Of course, the manual creation of such a complex tree would have been very difficult.

The analysis of this tree gives some interesting results. First, all nine hydrocarbons, obtained experimentally, were predicted by the FLAMINGOES program system among the 48 potentially possible products. Second, increasing the number of search stages up to eight does not lead to any structure that has not already been considered during previous stages. Thus, this tree is complete and includes all the intermediates and products that are possible in the given reactions. Last, but not least, the computer generation of similar trees for various subsets of admissible mechanistic pathways, namely, for either the anionic or radical reactions, led to only a limited set of isolated products, while the consideration of both mechanisms led to the real set of products. Thus, it is possible to select mechanistic pathways leading to the particular products and, consequently, to draw a conclusion about the general mechanistic picture of the investigated process.

In general, revelation of the sequence of complex, multistage reactions, especially those including rearrangement processes, is the advantage of the application of the FLAMINGOES program system.

## VII. CONCLUSION

The FLAMINGOES program described in this paper seems to be very promising for the solution of those problems of organic chemistry that can be formalized as the generation of all possible bond redistributions in a given structure(s). This program is an original computer system in the field of non-empirical computer-assisted synthesis. The construction of the FLAMINGOES program permits future development by the addition of some empirical selection criteria and empirical chemical information. In our opinion, the present version of this system can serve as a daily instrument for chemists interested in synthesis design, rearrangement processes, and, to some extent, reaction mechanisms.

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- Some of the types of organic reactions are not described as the CBR, but in the terms of the bond redistributions (BR) with more complex topologies. We developed the SYMBEQ program that can generate all the possible types of reactions for any given topology. So, with the help of the SYMBEQ program it is possible to make a search for principally novel organic reactions, especially with unusual topologies of BR. See also: Baskin, I. I.; Tratch, S. S.; Zefirov, N. S. "The Program of the Search for New Reaction Types of Organic Compounds by the Microcomputing Iskra-226". *Proceedings of the 7th Conference on Application of the Computers in Chemical Research and Molecular Spectroscopy*; Institute of Organic Synthesis, Academy of Sciences of Latv. SSR: Riga, 1986; pp 88-90.
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  - (27) It should be mentioned that our main purpose was to demonstrate the advantages of the program rather than to carry out a complete literature search for every aspect of considered chemical problems. We shall be thankful for any additional information about the practical realization of the processes proposed by FLAMINGOES program system.
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