Investigation of Carbocationic Rearrangements by the ICAR Program

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The ICAR program for the elucidation of carbocationic rearrangement mechanisms is described. Chemical transformations of the given structure are generated by an exhaustive combinatorial procedure and subsequently evaluated with the use of a knowledge base. Multistep mechanistic pathways are rationalized with regard to thermodynamic and kinetic parameters of the rearrangements. Application of the program is discussed.

INTRODUCTION

Elucidation of chemical reaction mechanisms still remains an important scientific problem, attracting the attention of many academic as well as industrial researchers.[1] Besides its evident fundamental character, the knowledge of reaction mechanisms is important for practical purposes, e.g., it may suggest how to change the conditions in order to alter the course of the reaction or to optimize its yield. The routine is as follows: chemists set up a few hypotheses by intuition and then prove or disprove them by experiments. The use of a computer permits the chemist to get rid of time-consuming manual consideration of possible multistep mechanisms, leaving the chemist only the general formulation of the problem and evaluation of results.

A number of computer systems have been already developed to automatize the problem of mechanism elucidation. The CAMEO computer program was developed to predict the products of organic reactions, given the starting compounds and reaction conditions as the input.[2] Chemical transformations are derived with the use of concise mechanistic rules, which cover the major types of organic reactions. A very diverse and sophisticated evaluation system allows one to determine the most favorable course of the reaction, i.e., to choose among possible competitive transformations of the same molecule. The RAIN program,[3] which is based on the Ugi–Dugundji algebraic theory,[4a] allows one to determine the shortest mechanistic pathways joining the given sets of reactants and products. Unlike CAMEO, the essence of RAIN is not to rely on previous experience, but to search for novel reactions, using elementary chemical knowledge. The inevitable combinatorial abundance of the problem is handled with the use of the minimum chemical distance principle.[4b] This allows the program to look for the shortest pathways in the uncertain space of possible solutions. A similar general strategy is applied in the MECHEM program.[5] An important feature of MECHEM is that the total stoichiometry need not be specified for the reaction. Just on the contrary, the program can search for the optimal stoichiometry, e.g., what provides for the best yield of the products.

Our research was focused as investigating mechanisms of carbocationic rearrangements. As important intermediates in many organic reactions, carbocations captured significant attention of many organic chemists.[6a] Transformations of

these highly reactive species can be effectively used in organic synthesis for complication and modification of molecular skeleton. Even many metabolic reactions, e.g., syntheses of most natural sesquiterpenoids, proceed *via* the cyclization of allylic cations, which result from enzyme-catalyzed ionization of unsaturated alcohol pyrophosphates.[6b] At the same time, mechanisms of these rearrangements can be very complicated, thus necessitating the use of a computer for their investigation. First attempts were undertaken at the end of 60s, when it was demonstrated that the rearrangements can be treated systematically by means of a reaction graph.[7a] Each vertex of this graph corresponds to a certain intermediate, while the edge connecting two vertices denotes the possibility of their mutual interconversion. This approach allowed to describe the rearrangements of various tricyclo-decane ($C_{10}H_{16}$) isomers in order to find possible multistep mechanisms of the twistane to adamantane rearrangement. Consideration of thermodynamic[7b,c] and kinetic[7d] features of these mechanisms allowed to select the most favorable rearrangement pathways.

Considering the importance of the problem, we developed the ICAR program[8] which combines exhaustive combinatorial search over the space of conceivable pathways with a flexible and highly interactive system of empirical selection criteria. The first feature ensures that any true mechanism of the rearrangement, whatever it is, theoretically can be found by ICAR. That is, no formally possible solution can be overlooked by the program, in contrast to the human brain. The second of the above features means the possibility to effectively eliminate the rest of pathways. In the following discussion, we briefly describe the program components and its application.

DESCRIPTION OF THE ALGORITHM

The general methodology of ICAR is similar to that of other programs designed for elucidating reaction mechanisms.[3,7e] Initially, the reaction graph that includes multistep rearrangements of the starting structure is constructed by the program. At the second step, rearrangement mechanisms, which correspond to paths within this graph, are generated by the conventional depth first search.
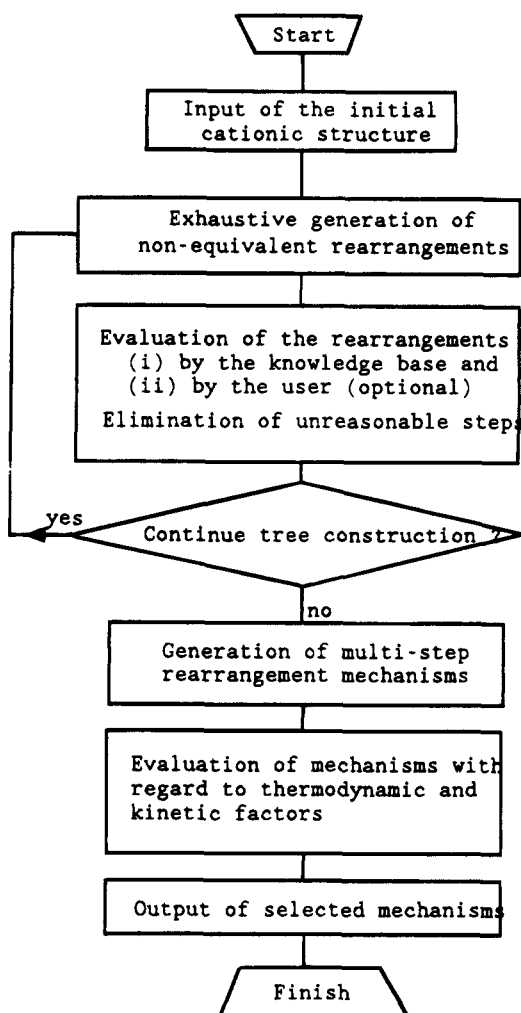
The flow chart of the program (Scheme 1) can be divided into four principal parts:

Input of the starting structure as a 2D sketch with the use of a graphical mouse-driven interface

Generation of one-step rearrangements of this structure

Scheme 1. General Flow Chart of ICAR

Table 1. Basic Types of Carbocationic Rearrangements

Evaluation of structural and energetic plausibility of these rearrangements aimed at discarding *a priori* unreasonable results

Recursive application of the second and third steps generates the reaction network, which is subsequently searched for possible multistep mechanisms

Combinatorial Enumeration of All Possible Rearrangements. The four known types of carbocationic rearrangements[1c] are given in Table 1. As can be concluded from Table 1; all the rearrangements can be described as migration of a single bond in the cationic structure to the carbonium center. The multiplicity of the migrating bond in the initial structure decreases by one, and the carbonium center is transferred to the atom at the disconnected bond. Structures are presented as graphs, and all operations are done with their connectivity tables. For symmetrical graphs (i.e., for those whose automorphism group includes more than one permutation) the constitutional symmetry should be considered to preclude the generation of equivalent bond migrations. The program evaluates the graph automorphism group and separates edges into equivalence classes. Transpositions of only one representative of each equivalence class are considered afterwards.

Evaluation of Rearrangements with the Use of a Knowledge Base. The generation of rearrangements by the formal procedure would inevitably produce implausible solutions, creating the need for the introduction of chemical reasoning in the program. To elaborate a uniquely defined

set of selection criteria is impossible, since principles of the selection depend on the reaction conditions, the chemists preferences, etc. The implementation of the selection criteria should be versatile enough to enable facile formalization of empirical knowledge required for the solution of a specified chemical problem and for interactive modification of the selection criteria.

Empirical knowledge can be introduced into the program in two different ways. The knowledge can be translated into commands of a high-level computer language and incorporated directly into the source code. In ICAR, however, the knowledge is stored in an external knowledge base in the form of some rules. Each rule comprises a number of logical tests (e.g., for the occurrence or count of a specified substructure) joined by Boolean operations and an integer rating value which is assigned to the examined rearrangement if the logical expression is fulfilled. Zero rating means that the reaction violates the selection principles and therefore should be eliminated. For instance, a number of commonly used rules discard structures which contain forbidden fragments, e.g., highly strained small rings.

The program can be run either in the automatic or in the interactive mode. In the latter case, the user is allowed to discard unreasonable solutions and to introduce new selection rules that will be used in subsequent runs. Manual evaluation of numerous structures is a tedious procedure; it is only used to account for the selection criteria which cannot be formalized or for the development of selection rules.

Evaluation of Rearrangements by Molecular Mechanics Calculations. Application of a knowledge base permits effective elimination of the reactions that are expected to be implausible due to quantitative considerations; however, a rigorous examination by empirical or quantum chemistry methods is required. The principal energy parameters to be taken into account are the free energy of the reaction and the free energy of activation ($\Delta G^{\ddagger}$), which correspond to the thermodynamic and kinetic control of the rearrangement, respectively. The former parameter can be accepted as the difference between the enthalpy of formation (ΔH_f°) of the initial and rearranged cationic structures. Application of

Table 2. The Λ_o Parameters (kcal·mol^{-1}) for the 1,2-Shifts from Ref[5a]

migrant	H	H	H	CH$_3$	CH$_3$	CH$_3$	C–C	C–C	C–C
type of rearrngmnt[a]	T–T	S–S	T–S S–T	T–T	S–S	T–S S–T	T–T	S–S	T–S S–T
Λ_o	6.6	10.5	10.2	8.2	13.3	8.3	3.8	3.8	5.0

[a] T and S denote tertiary and secondary carbocations, respectively.

semiempirical quantum chemistry packages or of the MM2 program with special force field parameters[9] provides a fast and reliable estimate of $\Delta H_f°$ values.

The evaluation of kinetic barriers is a much more complicated question. The direct approach, based on quantum chemistry calculations of the potential energy hypersurface, seems to be impracticable for screening a large number of structures. Transition state energies for 1,2-shift rearrangements can be roughly compared considering the angles between the vacant orbit of the carbonium center and the migrating σ-bond.[7d] This method is simple, but it does not give a quantitative estimate of the barrier and it also ignores some important factors, e.g., the difference in the migration aptitude of various bond types. Therefore, we used another approach, proposed by Barkhash *et al.*[10] on the basis of the Marcus equation,[11] for evaluating the barriers of 1,2-shifts ($\Delta G^{\ddagger}$)

$$\Delta G^{\ddagger} = \Lambda(1 - \Delta H_f°/4\Lambda)^2$$

$$\Lambda = \Lambda_0 \cos \varphi$$

where $\Delta H_f°$ is the enthalpy of the rearrangement, φ is the orbital angle, and Λ_0 is the internal barrier for $\Delta H_f° = 0$ and $\varphi = 0$. Values of Λ_0 for various types of migrating bonds derived from experimental data are given in Table 2.

Generation of Rearrangement Mechanisms. Recursive application of the "generate and check" procedure to each of the intermediates obtained at the *i*th step generates structures which can be formed at the $(i + 1)$st step. This stage is repeated until no further intermediates are found or user-defined terminal conditions are satisfied. For instance, the user may restrict the maximum number of steps along the tree.

Obviously, one and the same intermediate can be obtained by different ways and at different steps. These duplicates are detected in the reaction graph, and their subsequent rearrangements are no longer considered. Each new structure is mapped into a numeric index, and the program consults the internal table if any structures with the same index value have been previously generated. If any such structures are found, they are checked for isomorphism with the current one by a rigorous atom-by-atom mapping technique. This is a computationally intensive procedure, but it is rather seldom used, so the total slowing down of performance is negligible.

After the reaction graph is constructed, multistep pathways between any two given vertices can be found. The efficiency of the searching procedure can be improved by the elimination of the vertices that correspond to duplicate structures. The compressed graph obtained in this way contains loops, and its edges can be ordinary or directed, if they denote reversible and irreversible rearrangement steps, respectively.

The length of the shortest pathway between the starting and the final structure can be estimated in accordance with the principle of minimum chemical distance.[4b] However,

the chemically reasonable mechanisms can be essentially longer than the shortest ones, due to structural and energy considerations. The necessity of considering longer pathways increases the computational expenses, because the number of intermediates grows geometrically from step to step. Handling the inherent combinatorics is a real problem, which can be partially solved by careful formulation of the selection criteria and by their application at the earliest possible step. Another way to improve the efficiency, which is implemented in ICAR, is to generate two smaller trees separately from the starting and from the terminal structure, as is done by the RAIN program.[3] Concerted application of the sufficient restrictions allows the program to push back the point at which the combinatorial growth overwhelms the available computational resources and thus to enable solution of many practically significant problems.

Pathways generated by ICAR are sorted by their length. Approximate 3D models of structures are constructed by MOLGEO,[12] which performs 2D → 3D conversion of structures presented by graphs, preserving all stereochemical designations (*R/S, E/Z* configurations of chiral centers and double bonds, respectively) if any are given. The models are then refined by MM2 or MOPAC, giving also the energy parameters ($\Delta G^{\ddagger}$ and $\Delta H_f°$) of single rearrangement steps. Mechanisms that include steps with high $\Delta H_f°$ or $\Delta G^{\ddagger}$ values are eliminated as unfavorable. The maximum allowed $\Delta H_f°$ and $\Delta G^{\ddagger}$ values are chosen by the chemist and depend on the reaction conditions (temperature, solvent, etc). Finally, the selected mechanisms are visualized at the computer screen or output to a graphics printer.

EXAMPLES

The following discussion demonstrates the ability of ICAR to solve chemical problems. Additional examples can be found in ref 8a—e.

(1) Cyclization of Nerolidol Stereoisomers in Super-acids. Cyclization of *cis*- and *trans*- isomers of nerolidol (1) in HSO$_3$F−SO$_2$FCl at −110 °C gives tricyclic products 2 and 3 shown in Scheme 2.[8c] The problem is to suggest appropriate cyclization mechanisms for 1. The computer experiment was undertaken after all the attempts to find any reasonable cyclization mechanisms manually failed.

The following selection rules were put into the knowledge base. (a) Since intramolecular rearrangements were of major interest, only those transformations were accepted which did not result in fragmentation of the whole structure. (b) Only 1,2-shifts of the C−C and C−H bonds were considered to be possible. Shifts of σ-bonds to distant atoms were discarded. (c) Rearrangements which produced unstable primary cations, vinylic cations, or structures containing small rings as well as mono- or disubstituted double bonds (RCH=CH$_2$, R$_1$R$_2$C=CH$_2$) were eliminated. (d) 1,2-Shifts of a σ-bond in stable allylic cations were disallowed.

Scheme 2
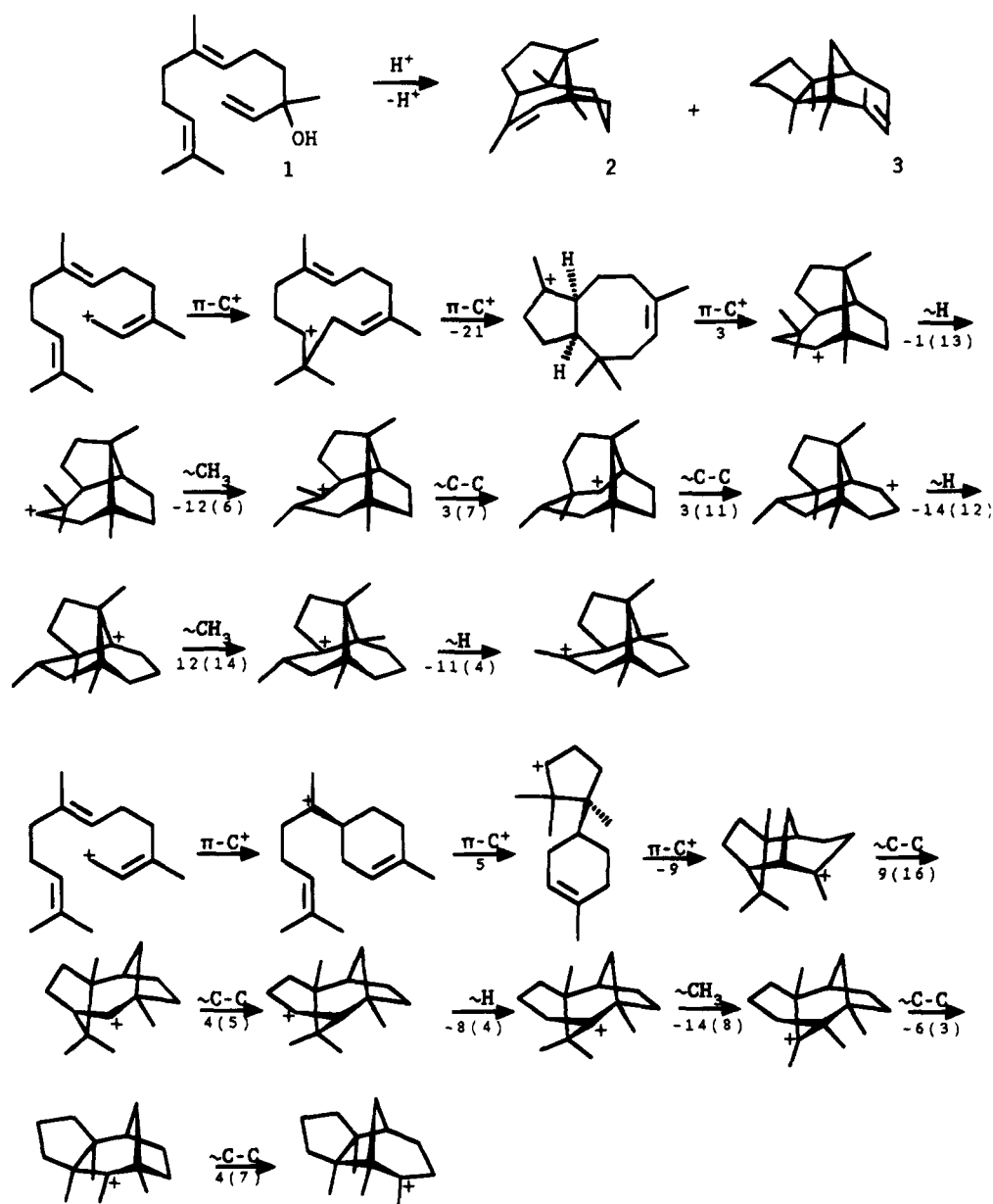
The most favorable formation mechanisms for the carbon skeletons of **2** and **3** are given in Scheme 2. The differences between the enthalpies of formation ($\Delta H_f{}^\circ$, kcal/mol) and the values of kinetic barriers ($\Delta G^{\ddagger}$, kcal/mol, in parentheses) are given under arrows. As was shown in literature, the cyclization of **1** in soft acids[13] produces a number of monocyclic and bicyclic structures similar to the intermediates that are formed at the initial steps of the mechanisms in Scheme 2. In the superacidic medium, these intermediates are evidently involved in subsequent transformations leading to the final tricyclic products **2** and **3**.

(2) Degenerate Rearrangements of the Nortricyclyl Cation. Experimental studies[14] revealed that degenerate rearrangements of the nortricyclyl cation (**4**) result in the scrambling of the ^{13}C label over all nonequivalent carbons: C(1), C(3), C(4), C(5), and C(6). However, the redistribution of other carbons in the rearrangements was not clear from the data in ref 14. To distinguish these carbons, let us assign a unique label to each of them, thus giving rise to 2520 different labeled structures (see Appendix). Possible interconversions between these structures were found by ICAR.
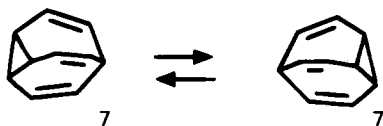
Chart 1

Only a very restricted set of rearrangements was allowed, since their possibility was experimentally confirmed: (A) the degenerate 1,3-hydride shift in **4**; (B) the β-fragmentation of **4** leading to the 2-norbornenyl cation (**5**); (C) the degenerate 1,2-hydride shift in **5**; (D) the skeletal rearrangement of **5** to the bicyclo[3.1.1]heptenyl cation (**6**); and (E) the allylic rearrangement of **6**. The program showed that the reaction graph containing all the 2520 labeled structures and possible intermediates is connected, i.e., any two structures are interconvertible. Therefore, the rearrangement of the nortricyclyl cation can be referred to as a *completely degenerate* rearrangement. A well-known example of such reactions is the degenerate Cope rearrangement of bullvalene (**7**), which includes interconversions between all the 604 800

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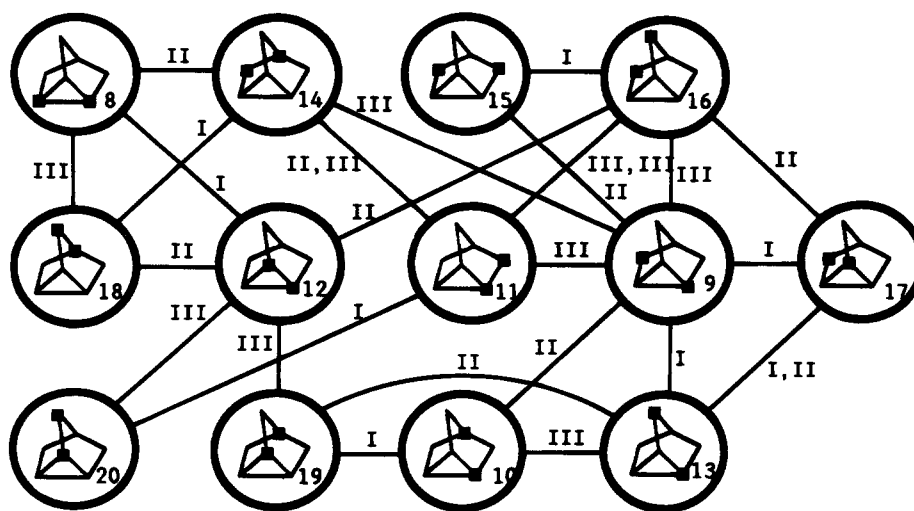
Chart 2

tautomeric forms of this molecule.[1c]

Since the reaction graph for the nortricyclyl cation is too big to be visualized, we give an example of the smaller graph for nortricyclyl cations with only two isotropic labels (Chart 2). Vertices of the graph correspond to 13 di-^{13}C-labeled structures (see Appendix), where the isotropic labels are shown as black squares. Roman figures above the edges of the graph denote types of rearrangement processes, which may include more than one step designated in Chart 1 as A—E (note: each letter denotes both direct and reverse rearrangements). There are three sequences of these steps leading from one nortricyclyl structure to another one: I; A; II; BCB; III; BDDB or BDEDB. Kinetic rates of these rearrangements are very different.[14] At temperatures below −70 °C, the contribution of rearrangements I and II is negligible, and the connected reaction graph is separated into six subgraphs containing the following sets of structures: {15}, {8,18}, {10,13}, {17}, {12,20,19}, and {9,11,14,16}. Since the structures from different sets are not interconvertible, only partial carbon scrambling occurs at very low temperatures. The same conclusion was made by the authors of ref 11 on the basis of experimental data.

CONCLUSION

ICAR is written in C following ANSI standards. The program requires an IBM PC compatible computer and is supplied with mouse-driven graphics interface.

To get an IBM PC version of the ICAR program, please contact Prof. Steve R. Heller: Research Leader Model and Database Coordination Lab., Agricult. Research Service, BARC-W, Beltsville, MD 20705, U.S.A.

ACKNOWLEDGMENT

APPENDIX

There are $N!/|\text{Aut}(G)|$ labelings of an N-vertex graph G by N different labels; $|\text{Aut}(G)|$ is the order of the automorphism group of G.[15] The automorphism group of the nortricyclyl cation graph (**4**) consists of two permutations: (1) (2) (3) (4) (5) (6) (7) and (12) (37) (4) (5) (6); therefore, **4** can be labeled in $7!/2 = 2520$ different ways.

For an arbitrary set of labels, the number of labelings can be evaluated by Polya's theorem:

(i) The cycle index Z of the Aut(G) group is

$$Z(\text{Aut}(G)) = \frac{1}{2}(a_1^7 + a_1^3 a_2^2)$$

(ii) The series z which enumerates labels on vertices of G is

$$z(x,y) = x + y$$

where x and y denote ^{12}C and ^{13}C atoms, respectively.

(iii) The substitution of a_1 and a_2 in the cycle index Z by z gives series C which enumerates labeled graphs:

$$C(x,y) = x^7 + 5x^6 y + 13x^5 y^2 + 21x^4 y^3 + 21x^3 y^4 + 13x^2 y^5 + 5xy^6 + y^7$$

The polynomial coefficient at $x^n y^m$ equals the number of structures containing n ^{12}C and m ^{13}C atoms; therefore, there are 13 structures containing two labels.

A theorem providing the necessary and sufficient condition for a reaction graph of a degenerate rearrangement to be connected was given by Klin and Zefirov in ref 16. However, this theorem can be applied only to those reaction graphs where every edge represents a rearrangement of the same type. Due to this reason, it cannot be used for investigating the connectivity of the nortricyclyl graph, where edges correspond to different rearrangements.

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