Approaching Problems of Molecular Design with the Aid of the Computer. 16. Application of the FLAMINGOES Program System to Selected Synthetic Problems

Nikolai S. Zefirov* and Ekaterina V. Gordeeva

N. D. Zelinsky Institute of Organic Chemistry, Leninsky Prospekt 47, Moscow, 117913 USSR

Received May 27, 1987

The previously developed FLAMINGOES program system was applied to the computer investigation of the following problems: (i) the search for possible strategic synthetic entries into three cage structures, bicyclo[1.1.1]pentane, tetracyclo[$3.3.0^{2,4}.0^{3,6}$]oct-7-ene, and hexacyclo[$4.4.0.0^{2,4}.0^{3,10}.0^{5,8}.0^{7,9}$]decane; and (ii) the search for possible precursors of the 2-norbornyl cation via skeletal rearrangement pathways. The program has reproduced the existing pathways and proposed many uninvestigated but promising transformations of the considered structures. Some general principles of the interpretation of the chemical information in the FLAMINGOES program system are briefly described.

I. Introduction

In spite of the declared "computer age" in chemistry[1a] and of the wide expansion of the programs for computer-assisted synthesis,[1b] the majority of organic chemists still regard the possibility of using the computer in routine work with trepidation. In our opinion this situation is, at least in part, due to the fact that the scientists who are working in the field of computer-assisted synthesis usually publish the general principles of their programs rather than the results of the computer search using these programs. In turn, the chemists who want to use the computer prefer not to see the general principles supplemented with occasional results of computer-assisted syntheses but instead significant quantities of convincing examples of computer applications in organic chemistry. However the publication of results generated with the computer is difficult owing to the following situation. Any kind of program for a computer-assisted synthesis usually generates two extreme kinds of conclusions: (i) precedented chemistry and (ii) unprecedented chemistry. The former results are those which have been published previously; the latter ones, which are probably the most interesting, cannot be published because the "predictions" of possible synthetic pathways unfortunately are not traditional in articles in organic chemistry.

Taking this into account, we decided to attempt to attract the attention of chemists to our multipurpose FLAMINGOES program system[2] by the demonstration of the results directly generated by this program. We believe that articles which contain the schemes of transformations as predicted by the computer, supplemented with only a short description of the introduced information and minor comments on the chemistry, can be a valuable aid to experimental organic chemists. To be honest we shall present all, except where noted, generated results and even those omissions in the schemes are commented on.[3]

II. Brief Introduction to the Terminology Used in the FLAMINGOES System

The FLAMINGOES program system is a nonempirical program for computer-assisted synthesis,[1b] and it does not use any data bases during its operation. This system generates a set of precursors based on the formal-logical approach to organic reactions.[4–10] in which the reactions are represented as cyclic redistributions of bonds.

For man–machine communications the chemist must take into account a few notations that are used for subsequent discussions and formal presentation of organic molecules and reactions in the program: (a) *initial chemical system* is a goal structure or set of structures in which the reactions (or rearrangements) are generated; (b) *final chemical systems* are the structures which are found during the computer search; (c) *choice of admissible reaction types* which are made by the chemist via dialogue and permits (1) *choice of admitted sizes* of cyclic bond redistributions and (2) *choice of number of bonds*, which are broken or formed in the course of the reactions; (d) *choice of potential reaction centers*, which means the choice of those atoms or atom groups in the initial chemical system for which the number and/or multiplicity of the bonds can, in principle, be changed during the possible reactions. The latter criteria can be introduced to limit the enormously large amount of the formally possible but chemically noninteresting or naive results.

III. The Computer Search for Strategic Synthetic Pathways to Selected Cage Structures

Cage structures, especially the strained ones, have attracted the attention of chemists for a long time. The problem of finding elegant or original synthetic entries into the cage polycyclic hydrocarbons is extremely attractive.

The cage structures are of great interest also from the point of combinatorial enumeration of chemical objects. One of the first examples in this area is illustrated by Balaban's work[11–13] which dealt with the problem of exhaustive generation of all possible valence isomers of annulenes. One of us carried out the *constructive* enumeration of families of cage structures based on the principle of *isomorphic substitution*[14] that revealed non-self-evident

---

(1) (a) Haggin, J. *Chem. Eng. News.* **1983**, *61* (9), 7. (b) Zefirov, N. S.; Gordeeva, E. V. *Usp. Khim.* **1987**, *56*, 1753.

(2) (a) The general principles of FLAMINGOES (ref 2b) as well as the mathematical statement of the problem (ref 2c) were described previously. (b) Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.* **1981**, *17*, 2465. (c) Zefirov, N. S.; Gordeeva, E. V.; Tratch, S. S., submitted for publication in *J. Chem. Inf. Comput. Sci.*

(3) The complete set of computer pathways for each of the considered problems without selection criteria will be published separately in *Zh. Org. Khim.*

(4) For general review of formal-logical approach, see: Zefirov, N. S. *Acc. Chem. Res.* **1987**, *20*, 237.

(5) Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.* **1975**, *11*, 225.

(6) Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.* **1975**, *11*, 1785; **1984**, *20*, 1121.

(7) Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.* **1976**, *12*, 7.

(8) Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.* **1976**, *12*, 697.

(9) Zefirov, N. S.; Tratch, S. S. *Chem. Scr.* **1980**, *15*, 4.

(10) Tratch, S. S.; Zefirov, N. S. *Zh. Org. Khim.* **1982**, *18*, 1561.

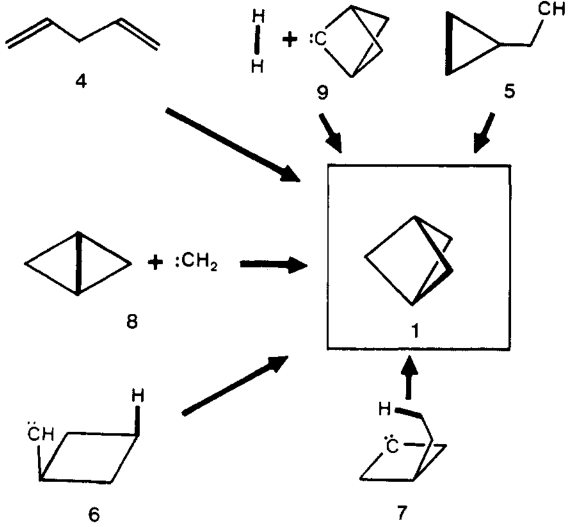
(11) Balaban, A. T. *Rev. Roum. Chim.* **1966**, *11*, 1097.

(12) Balaban, A. T. *Ibid.* **1970**, *15*, 463.

(13) Balaban, A. T. *Ibid.* **1972**, *17*, 865.

0022-3263/88/1953-0527$01.50/0

Scheme I. Pathways to Bicyclo[1.1.1]pentane via Cycloadditions and [1 + (1,1)]-Additions



structural relations among selected polycyclic hydrocarbons. The present report is the development of the combinatorial approach to the problem of cage structures from the point of a computer search for synthetic pathways to the target polycyclic skeletons.

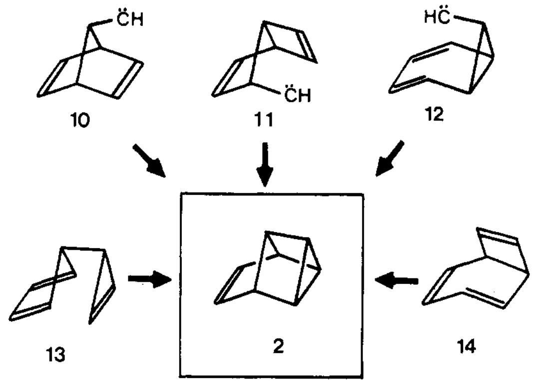
Three cage structures, bicyclo[1.1.1]pentane (1), tetracyclo[3.3.0^{2,4}.0^{3,6}]oct-7-ene (touristene, 2), hexacyclo[4.4.0.0^{2,4}.0^{3,10}.0^{5,8}.0^{7,9}]decane (barettane, 3) were introduced in the FLAMINGOES program system in order to generate all possible one-stage strategic synthetic pathways and, hence, to demonstrate its possibilities. For each of the considered cage structures all the carbons and hydrogens were selected as potential reaction centers, and hence we did not introduce any limitation at this stage.

Taking into account that formation of a carbocyclic skeleton is usually the key stage in the synthesis we consider only the so-called strategic transformations, i.e., those leading to the manipulation of skeleton bonds of the target compounds. To find the strategic pathways to the proposed structures we use the following set of admissible reactions: [2 + 2]-, [4 + 2]-, [2 + 1]-, [4 + 1]-cycloadditions and the [1 + (1,1)]-addition process, i.e., the reaction of carbene insertion into an ordinary bond.

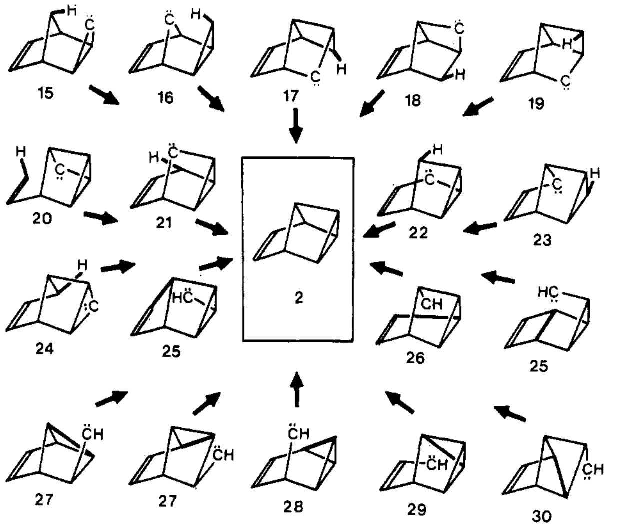
Indeed, cycloadditions seem to be very effective for the synthesis of cage skeletons. The idea of an elegant cycloaddition has a long history, including Woodward's suggestion to synthesize dodecahedrane from two molecules of triquinacene.[15,16] Moreover, the [4 + 2]-cycloaddition or Diels–Alder reaction is now probably one of the most important synthetic methods. For example, the LHASA system uses a strategy especially oriented to this reaction.[17] The [2 + 2]- and [2 + 1]-cycloadditions are also generally recognized.

The [4 + 1]-cycloaddition is rather unusual in actual practice, and examples therefore are rare (see, for instance, benzvalene formation from cyclopentadienyl carbene[18]).

Scheme II. The [2 + 1]-, [4 + 1]- and [4 + 2]-Cycloaddition Pathways to Touristene Structure



Scheme III. The [1 + (1,1)]-Addition Pathways to Touristene Structure



In fact the competitive processes of [2 + 1]-cycloaddition of carbene usually occur instead of [4 + 1]-cycloadditions. On the other hand, the resulting vinylcyclopropanes can further rearrange to give cyclopentenes and, hence, the total result can be described as a [4 + 1]-cycloaddition.

In spite of the low selectivity of carbene insertion into C–C and C–H bonds, these reactions were used in various syntheses for ring closure steps or expansion of carbocycles,[19] and we include the process of [1 + (1,1)]-addition (for the classification see ref 7) into the set of admissible reactions.

The results of the computer search for strategic synthetic pathways to 1 are presented in Scheme I. Only six possible variants for the synthesis of the target structure 1 were obtained by the computer (please, remember the restrictions of admissible reactions). As it is shown in Scheme I, there exists only one way to obtain 1 via [2 + 2]-cycloaddition (namely, 4 → 1). While this process is not self-evident, it reproduced the literature data: substituted bicyclo[1.1.1]pentanes were found among the products of irradiation of substituted 1,4-pentadienes.[20]

The other four possibilities in Scheme I represent different variants of the carbene insertion in the C–C and C–H bonds. The transformations 5 → 1, 6 → 1, 7 → 1 are of general interest. What is more, the pathway 8 → 1 has been already realized: dichlorocarbene inserts into the

---

(14) Zefirov, N. S.; Tratch, S. S.; Chizhov, O. S. *Cage and Polycyclic Compounds Molecular Design Based on the Principle of Isomorphic Substitution*, Itogi: Nauki Tekhniki, Seriya: Organicheskaya Khimiya; Mezhdunar Kniga: Moscow, 1979; Vol. 3, CA92(7):58259g.

(15) Woodward, R. B.; Fukunaga, T.; Kelly, R. C. *J. Am. Chem. Soc.* **1964**, *86*, 3162.

(16) For pioneering synthesis of dodecahedrane, see: Gallucci, J. C.; Doecke, C. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1986**, *108*, 1343.

(17) Corey, E. J.; Long, A. K.; Rubenstein, S. D. *Science (Washington, D.C.)* **1985**, *228*, 418.

(18) Burger, U.; Gandillon, G.; Mareda, J. *Helv. Chim. Acta* **1981**, *64*, 844.

(19) Carey, A. F.; Sundberg, R. J. *Advanced Organic Chemistry*; Academic: New York, 1978.

(20) Srinivasan, R. *J. Am. Chem. Soc.* **1968**, *90*, 2752.

central C–C bond of bicyclobutanes, activated by electron-withdrawing substituents.[21,22] It should be also noted that the transformation of type **7** → **1** has been attempted but, unfortunately, failed to produce the tetrahedrane structure.[23]

The strategic one-step pathways to the tetracyclic olefin **2** generated by the computer are depicted in Schemes II and III. Consider first the cycloaddition processes of Scheme II. The [2 + 1]-cycloaddition in **10** seems to be much more promising than the analogous process in **11**. In fact, the transformation **10** → **2** has been reported in the literature.[24] The intramolecular cycloaddition in **11** could also be useful either for the precursor with protection of the one of double bonds or for the hydrogenated analogue of touristene, **2**. The transformation **12** → **2** includes the [4 + 1]-cycloaddition, which has not yet been investigated.

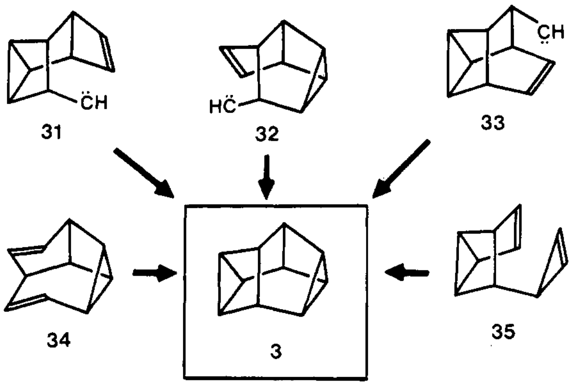
The **13** → **2** transformation in Scheme II is an intramolecular Diels–Alder reaction. There is indirect confirmation of the corresponding retro-process for the tetracyclo[3.3.0^{2,4}.0^{3,6}]oct-7-ene skeleton: it has been suggested that the thermolysis of **2** probably proceeds via the [4 + 2]-cyclofragmentation with the intermediacy of **13**.[25] One can assume that the direct conversion of **13** to **2** is also probable. The computer search demonstrates furthermore that system **13** has a second way to be transformed into the target skeleton, namely, via [2 + 2]-cycloaddition.

Among the variants of the [2 + 2]-cycloadditions, revealed by FLAMINGOES as the strategic synthetic pathway to **2**, the transformation **14** → **2** has been observed as an intermediate step in the photochemical interaction of disubstituted bicyclo[4.2.0]octa-2,4,7-triene, which can reversibly rearrange to the disubstituted touristene.[26]

Scheme III exhibits the group of pathways to **2**, which contains 18 transformations via carbene insertion into C–H and C–C bonds or [1 + (1,1)]-additions in terms of the formal-logical approach.[7–9] All depicted chemical systems represent rather complicated tricyclic structures. Generally speaking, some of transformations in Scheme III look unreasonable. However, we present the complete set of the results in order to demonstrate that FLAMINGOES can generate numerous decisions even with minor initial restrictions. There are only two points to be stressed. First of all, the attempt to synthesize **2** by the intramolecular carbene insertion into C–H bond (**15** → **2**) has been described in the literature.[27] Transformations **16** → **2** and **25** → **2** look analogously reasonable. Secondly, simple and effective selection criteria, decreasing the number of generated [1 + (1,1)]-transformations, could be easily elaborated. We will mention only that carbene insertions proceed smoothly for strained C–C bonds, e.g., in the cyclopropane fragment or in the diagonal bond in bicyclobutane.

For the described but still not available barettane (**3**), the FLAMINGOES program system generates five strategic synthetic pathways via cycloaddition reactions (Scheme IV). Though the structures **31**–**35** possess the complex tetracyclic skeleton, the multistage computer search must be done to find realistic precursors.[3]

Scheme IV. The [2 + 1]- and [2 + 2]-Cycloaddition Pathways to Barettane Structure



IV. The Computer Search for Precursors of 2-Norbornyl Cation via Skeletal Rearrangement Pathways

The 2-norbornyl cation is a structure, which has been in the focus of physical organic chemistry more than 20 years. A colossal amount of the literature, including monographs and reviews, has been devoted to the problems of generation, properties, and especially of the structure of this cation and its derivatives.[28–31] The discussion about the 2-norbornyl cation structure being either an equilibrium between two classical ions (proceeding via 1,2-shift) or the nonclassical ion, prompted investigations in the field of physical–organic chemistry. The norbornane structure has served as the favorite model for investigations of the skeletal rearrangements (for example, Wagner–Meerwein and Nametkin types).

Our approach to the problem of the 2-norbornyl cation (**36**) is nontraditional in the sense that it is not related to the problem of its fine structure. We tried to answer one question: from what precursors one can generate the 2-norbornyl cation via skeletal rearrangements or via the electrophilic addition of a cationic center to a double bond? In other words, our question focuses on precursors for the synthesis of norbornane skeleton via rearrangement pathways.

The usual route to 2-norbornyl cation formation is the heterolysis of the C2–X bond in the 2-substituted norbornanes. Second, there is a well-known pathway for the generation of **36** from derivatives of bicyclo[3.1.1]heptane via a 1,2-shift in the corresponding carbocation.[32,33] Third, the so-called "π-route" to the 2-norbornyl cation from β-ethyl-substituted cyclopentene was proposed,[34,35] starting from the assumption about the nonclassical structure of **36**. Evidently the above-mentioned rearrangements do not represent all possible ways of generation of **36**; however, we have not found the exhaustive solution of this problem in the literature.

In general, constructive enumeration of all possible rearrangement pathways leading to a given cation is not simple because carbocations are extremely reactive species, and many π- and σ-bonds in their structures can, in

---

[21] Applequist, D. E.; Renken, T. H. *J. Org. Chem.* **1982**, *47*, 4985.

[22] Grigor'ev, A. E.; Tarakanova, A. V.; Mil'vitskaya, E. M.; Pisanov, N. V.; Morozova, N. M.; Plate, A. F. *Vestn. Mosk. Univ., Ser 2: Khim.* **1980**, *21*, 498.

[23] Shelvin, P. B.; Wolf, A. P. *J. Am. Chem. Soc.* **1970**, *92*, 406.

[24] Stapersma, J.; Rood, I. D.; Klumpp, G. W. *Tetrahedron* **1982**, *38*, 191.

[25] Klumpp, G. W.; Stapersma, J. *J. Chem. Soc., Chem. Commun.* **1980**, 670.

[26] Tinnemans, A.; Neckers, D. C. *Tetrahedron Lett.* **1978**, 1713.

[27] Klumpp, G. W.; van Dijk, P. M. *Recl. Trav. Chim. Pays-Bas* **1979**, *90*, 381.

[28] Brown, H. C.; Schleyer, P. v. R. *The Nonclassical Ion Problem*; Plenum: New York 1977.

[29] Olah, G. A.; Prakash, G. K. S.; Saunders, M. *Acc. Chem. Res.* **1983**, *16*, 440.

[30] Walling, C. *Acc. Chem. Res.* **1983**, *16*, 448.

[31] Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426.

[32] Wagner, G.; Brickner, W. *Ber.* **1899**, *32*, 2302.

[33] Meerwein, H.; Vorster, J. *J. Prakt. Chem.* **1937**, *B147*, 83.

[34] Bartlett, P. D.; Sargent, G. D. *J. Am. Chem. Soc.* **1965**, *87*, 1297.

[35] Moreover, the presence of the rearranged substances is often considered as a forcible argument for the carbocationic character of the process (see, for example: Betel, D.; Gold, V. *Carbonium Ions. An Introduction*; Academic: New York, 1967.

principle, be involved in the rearrangement process. The complexity and variability of reactions proceeding via carbocationic transformations necessitate a computer application. Such examples as the creation and analysis of rearrangement processes in the "adamantane-land", as carried out by Schleyer et al.,[36-39] and the manipulation with the "map of the possible molecular rearrangements of substituted cariolanes in superacids", which was done by Koptyug et al.,[40,41] demonstrate the promising possibilities of the enumeration approach to selected carbocation problems.

The present section is devoted to the problem of finding all the cationic structures which are capable of rearranging into the 2-norbornyl cation via one- or two-stage skeletal rearrangement, using FLAMINGOES. In other words we consider the creation of "norbornyl cation land".

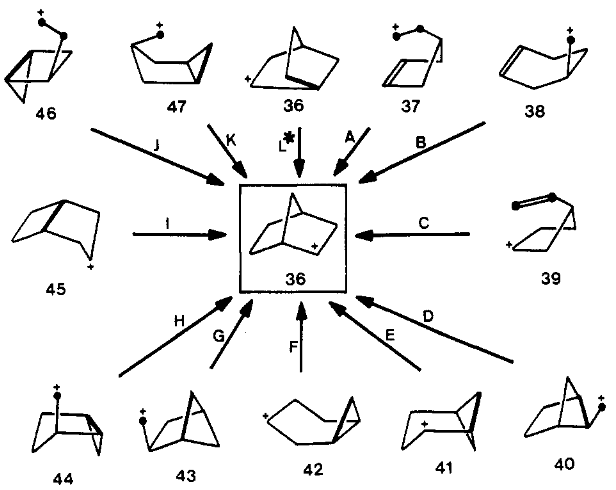
Let us describe the FLAMINGOES operation for that purpose in more detail. The initial chemical system **36** in the so-called "pseudocanonical form" (see ref 10) was introduced into the program with the positive charge at C2 presented as an independent potential reaction center ("phantom-center"[10]) being connected with C2 by a special "phantom-bond".[2] All the carbon atoms and the phantom-center (+) were selected as potential reaction centers. In other words we did not consider the rearrangements in which hydrogen atoms took part (H-shift). While hydride migrations are well-known for this system and have even been investigated by the computer,[42-44] the emphasis of our approach is to consider only those transformations in which the bicyclic skeleton **36** is formed. During the computer search the program actually generates the "antithetic" transformations, i.e., the reverse reactions, going back from the cation **36** to its precursors. Each of the cations generated at the first stage was introduced, in turn, as the initial chemical system for the second stage in order to generate a complete set of all possible precursors of **36** for two-stage processes.

The following two types of transformations were included in the set of admissible reactions: (a) 1,n-shift of C–C bonds; (b) electrophilic addition of the carbocation center to the double bond. We have arbitrarily chosen that for a given problem the value n can be varied from 2 to 4 ($n = 2, 3, 4$), because the probability of 1,n-shifts were $n > 4$ is low.

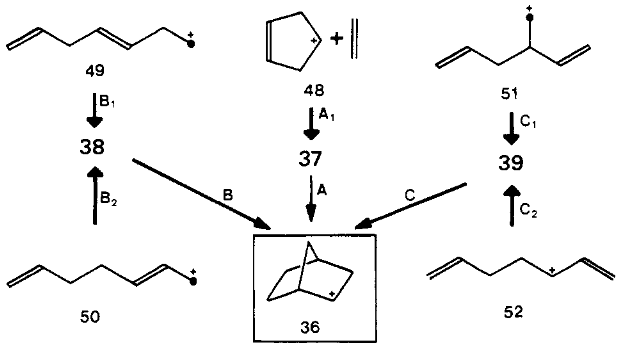
The following general factors for monitoring the probability of the realization of a particular reaction have been considered in order to work out the appropriate evaluation criteria implemented in the program. Consider first the electronic factors:

(I) The transformation should proceed from less substituted carbocations to a more substituted one. The following rating of transformations was chosen. The most profitable transformation of a primary carbocation into a secondary one is marked by [+]. The other types were (i) secondary cation to secondary one, [+ –], (ii) primary cation to primary one, [– +], and (iii) secondary cation to primary one, [–].

Scheme V. The One-Stage π- and σ-Routes to Norbornyl Cation Structure



Scheme VI. The Two-Stage π,π-Routes to Norbornyl Cation Structure



(II) The addition should lead to the most substituted carbocationic center (the Markovnikov rule). If this rule is obeyed the process has a rating [+]. Otherwise the transformation has a rating [–].

(III) The remoteness of the shifted bond from the carbocationic center is of importance. We have chosen the following scale of rating: the most probable is the 1,2-shift, [+], while 1,3- ([+ –]) and 1,4-shifts ([– +]) are less probable.

(IV) The strain of the shifted C–C bond was also evaluated. We introduced the following scale of rating: the shift of the most strained bond, i.e., one in a three-membered ring, gets the highest rating, [+], and then, in order, the σ-shifts in four-membered ([+ –]), in five-membered ([– +]), and in six-membered cycle or in the acyclic fragment ([–]).

(V) To evaluate the probability of σ-shifts in the unsaturated systems we took into account the following additional factor: the σ-shift of a C–C bond is less probable from an atom in sp^2-hybridization. We introduced the following scale of rating for C–C bonds: the most probable σ-shift of sp^3–sp^3 bonds gets the rating [+], the less probable shifts of sp^3–sp^2 and sp^2–sp^2 bonds get the rating [– +] and [–], respectively.

Twelve one-stage and 71 two-stage rearrangement pathways to the 2-norbornyl cation were generated by FLAMINGOES as well as 39 carbocationic structures, which are capable of rearranging into cation **36** via either σ-shifts

---

(36) Whitlock, H. W.; Siefken, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 4929.

(37) Engler, E. M.; Farcasiu, M.; Seven, A.; Cense, J. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 5769.

(38) Gund, T. M.; Schleyer, P. v. R.; Gund, P. H.; Wipke, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 743.

(39) Osawa, E.; Agami, K.; Takaishi, N.; Inamoto, Y.; Fujukura, Y.; Majerski, Z.; Schleyer, P. v. R.; Engler, E. M.; Farcasiu, M. *J. Am. Chem. Soc.* **1977**, *99*, 5361.

(40) Gatilova, V. P.; Korchagina, D. V.; Bagryanskaya, I. Yu.; Gatilov, Yu. V.; Dubovenko, Zh. V.; Barkhash, V. A.; Koptyug, V. A. *Zh. Org. Khim.* **1985**, *21*, 7.

(41) As the matter of fact, the possible π-routes to adamantane and diamantane have not been taken into consideration during the generation of the possible rearrangement processes (ref 36–38) while they could be promising.

(42) Johnson, C. K.; Collins, C. J. *J. Am. Chem. Soc.* **1973**, *95*, 4766.

(43) Johnson, C. K.; Collins, C. J. *J. Am. Chem. Soc.* **1974**, *96*, 2514.

(44) Johnson, C. K.; Collins, C. K. *J. Am. Chem. Soc.* **1974**, *96*, 2524.

(45) Sorensen, T. S. *Acc. Chem. Res.* **1976**, *9*, 257.

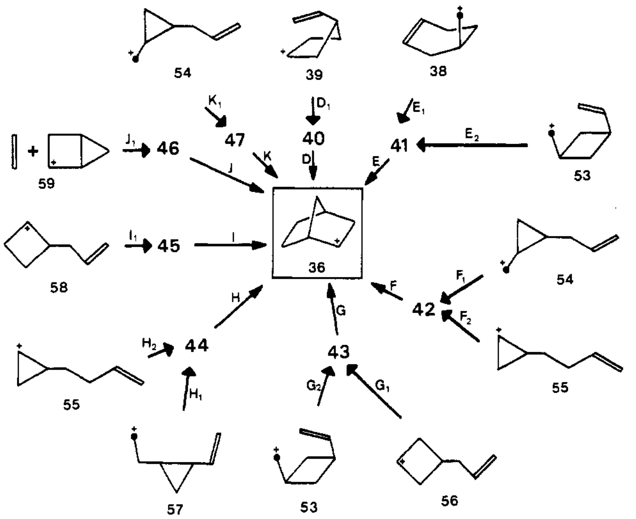
Table I. The Ratings of the Rearrangement Pathway to the 2-Norbornyl Cation

	the one-stage π- and σ-routes											
factor	A	B	C	D	E	F	G	H	I	J	K	L*
I	+	+	+−	+	+−	+−	+	+	+−	+	+	+−
II	+	+	+									
III				+	+	+−	+−	+−	+−	−+	−+	+
IV				+−	+−	+	+−	+	+−	+	+	−+

	the two-stage π,π- and π,σ-routes																
factor	A_1	B_1	B_2	C_1	C_2	D_1	E_1	E_2	F_1	F_2	G_1	G_2	H_1	H_2	I_1	J_1	K_1
I	−	−+	−+	+	+−	−	+	+	+	+−	−+	−+	−+	−	+−	−	−+
II	−	−	−	+	+	−	+	+	+	+	−	−	−	−	+	−	−

	the two-stage σ,π-routes												
factor	A_2*	A_3	A_4	B_3	B_4	B_5*	B_6*	B_7	C_3	C_4	C_5	C_6	C_7*
I	−+	−	−+	−	−	−+	−+	−+	+	+	+	+−	+−
III	+	+−	−+	+	+	+−	+−	−+	+	+	+−	+−	+−
IV	−	−	−	−	−	−	−	−+	+−	+−	+	+	−
V	+	+	−+	+	+	+	−+	−+	+	+	+	+	−+

Scheme VII. The Two-Stage π,σ-Routes to Norbornyl Cation Structure

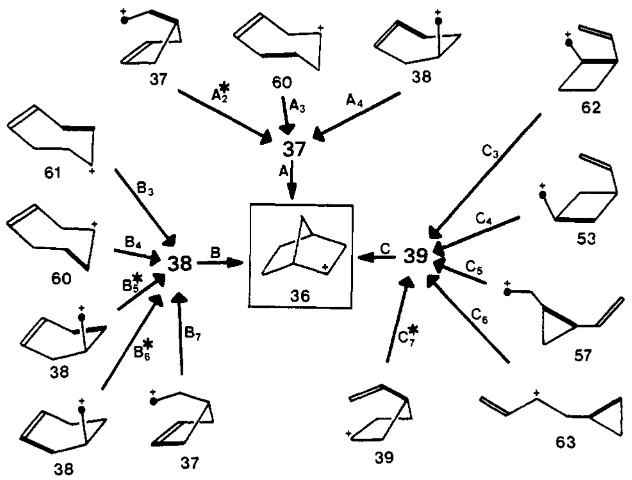


of C–C bonds and/or the electrophilic addition (Schemes V–VIII). The estimation of the generated pathways according to the introduced rating scale are given in Table I.

Consider first the one-stage skeletal rearrangements, which are given in Scheme V (shifted σ-bonds are marked by solid lines). The transformation L* (Wagner–Meerwein rearrangement) is the degenerate rearrangement in case of the unsubstituted 2-norbornyl cation (the degenerate rearrangements are marked by an asterisk), because the initial and resulting cations are distinguished only by numeration of the skeleton atoms. If this rearranged 2-norbornyl cation is, in turn, introduced as the initial chemical system in the second step of computer search the resulting scheme is identical with Scheme V with variation in atom numeration, which, by the way, confirms the correctness of a main combinatorial algorithm of the FLAMINGOES program.

Among predicted π-routes (Scheme V) pathways A and B are the most probable according to the introduced rating scale. Indeed, both of them were observed experimentally.[34,45] As a matter of fact, transformation B was also used as the key stage in the formation of the thiabicyclo[2.2.1]heptane skeleton.[46] The experimental proof of process C seems to be of unquestionable interest; this pathway can be considered as a computer prediction of novel π-route to 2-norbornyl cation.

Scheme VIII. The Two-Stage σ,π-Routes to Norbornyl Cation Structure



FLAMINGOES has found two possible σ-routes to the 2-norbornyl cation, proceeding as 1,2-shift of the C–C bonds (Scheme V, transformations D and E). The E route is a well-known rearrangement,[32,33] while the 1,2-shift in **40** (route D) seems to be not reported but nevertherless looks very promising. The next group of transformations includes the 1,3-shifts in carbocations **42–45**. According to the introduced rating the processes G and H are the most probable, especially the latter one, because the derivatives of bicyclo[3.1.0]heptane are well-known and available.

Each of the structures **37–47**, generated at first stage, was automatically introduced as the initial chemical system at the second stage of the computer search. We classify the resulting two-stage transformation as π,π- (double π), π,σ-, σ,π-, and σ,σ- (double σ) routes. Besides the σ,σ-routes,[3] all the others are depicted in Schemes VI and VII. First of all, consider the double π routes (Scheme VI). According to the ratings in Table I, the transformations C_1 and C_2 seem to be the most probable among the double π routes, and experimental realization of them looks very probable, especially in the case when the initial π system is installed in a rather rigid skeleton. The transformation A_1 in the two-component system **48** also seems promising if the potential homoallylic interaction in the cyclic component is minimized with proper substitution.

The cations **50** and **52** are the resonance structures of the same allylic cation. It should be noted that the resonance structures are interpreted by FLAMINGOES as indi-

---

(46) Gevaza, Yu. I.; Staninets, V. I. *Khim. Geterotsikl. Soedin.* **1986**, 291.

vidual chemical systems, and their interconversion is interpreted as the allylic "rearrangement".

Second, consider the π,σ-routes to the 2-norbornyl cation (Scheme VII). The most probable transformations according to the ratings in the Table I are the routes E_1, E_2, F_1, F_2, and I_1. It is interesting that monocyclic cation **38** can be a precursor of **36** both in the one-stage transformation (route B, Scheme V) and in the two-stage one (route E_1, Scheme VII): if the carbocationic center in **38** attacks the nearest end of the double bond the two-stage process should occur, while the one-stage pathway is possible if the remote end is attacked. The other π,σ-routes of Scheme VII include the anti-Markovnikov electrophilic addition and, hence, are less probable.

Route J_1 is a second example of the two-component electrophilic addition: the precursor **46** in this process is the product of intermolecular addition to bicyclopentenyl cation (cf. route A_1, Scheme VI).

All σ,π-routes, found by FLAMINGOES are depicted in Scheme VIII. These pathways include the σ-shift in the presence of the more nucleophilic double bond which extremely decreases the probability of these processes. Nevertherless the presented σ,π-routes can be of interest for systematic description of "norbornyl cation land" as well as for particular studies under conditions that impede the electrophilic addition in comparison with the σ-shift of a C–C bond.

V. Conclusion

The computer search for the strategic synthetic pathways to selected structures, which was carried out by the FLAMINGOES program system, demonstrates the possibility of finding rather interesting and promising results, based exlusively on a nonempirical approach to organic reactions. Moreover, the proposed strategies of syntheses might be particularly useful for the synthesis of heterocyclic analogues of those carbocyclic structures.

The computer search of the pathways to the 2-norbornyl cation demonstrates the variety of the skeletal rearrangements leading to this well-investigated system. During this search FLAMINGOES (i) reproduced the known routes to the 2-norbornyl cation and (ii) suggested many new precursors of different types. In our opinion, double π routes are of particular interest.

The present version of FLAMINGOES generates only the strategies of synthesis; generation of more detailed predictions probably needs an interaction with some empirical data base. We are planning to supplement our program system by a set of additional empirical selection criteria to make its predictions more precise. It should be mentioned that the FLAMINGOES is multipurpose system and it can be applied in solution of various problems, e.g., for mechanistic problems in organic chemistry.[47] The work presented in this report is only the first step in a long way to the creation of a highly developed apparatus of "artificial intellect" for the solution of synthesis and mechanistic problems in organic chemistry.

Acknowledgment. We are very grateful to Professor R. Caple for improving our manuscript and for stimulating discussions.

Registry No. 1, 311-75-1; 2, 35434-64-1; 3, 52674-19-8; 4, 24321-81-1.

---

(47) Zefirov, N. S.; Gordeeva, E. V.; Kuznetsova, T. S.; Kozhushkov, S. I. *Zh. Org. Khim.* **1988**, *24*, 36.

Tetra-*n*-butylammonium Oxone. Oxidations under Anhydrous Conditions

Barry M. Trost* and Rebecca Braslau

Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706

Received May 8, 1987

Tetra-*n*-butylammonium Oxone, readily prepared as a white solid from commercially available Oxone, performs oxidations in anhydrous methylene chloride. Under these conditions, sulfides are oxidized to sulfones in the presence of amines, ketones, esters, carbamates, olefins, and hydroxyl functionalities. Very acid-labile groups such as dimethyl ketals and THP ethers require buffering with anhydrous sodium carbonate. Reactions may be worked up either by direct chromatography of the reaction mixture or by two-phase aqueous extraction. Sulfur-containing amino acid derivatives are also oxidized under these conditions.

Our interest in the chemistry of acyl sulfones[1] led us to consider the possibility of their availability by oxidation of thio esters. The anticipated acylating activity of the product requires an oxidizing agent wherein neither the reagent itself nor its reduction products would be nucleophiles. The chemoselectivity of sulfide oxidations with Oxone (Du Pont), a ternary mixture of potassium hydrogen persulfate, potassium bisulfate, and potassium sulfate, turned our attention to this reagent;[2,3] however, the requirement of aqueous or alcoholic solvents had to be overcome. We have found that Tetra-*n*-butylammonium Oxone (TBA-OX) is a readily prepared white solid that may be used for oxidations under totally anhydrous conditions.

---

(1) Cf. Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469. Also see: Barton, D. H. R.; Manly, D. P.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1568. Schank, K.; Werner, F. *Liebigs Ann. Chem.* **1979**, 1977.

(2) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(3) For some recent work using Oxone as an oxidant, see: (a) Evans, T. L.; Grade, M. M. *Synth. Commun.* **1986**, *16*, 1207. (b) De Poorter, B.; Ricci, M.; Meunier, B. *Tetrahedron Lett.* **1985**, *26*, 4459. Dehmlow, E. V.; Vehre, B.; Makrandi, J. K. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1985**, *40B*, 1583. (d) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (e) Bloch, R.; Abecassis, J.; Hassan, D. *J. Org. Chem.* **1985**, *50*, 1544. (f) Jeyaraman, R.; Murray, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 2462. (g) Suryawanshi, S. N.; Fuchs, P. L. *Tetrahedron Lett.* **1981**, *22*, 4201.

(4) See reference 3a–c.

0022-3263/88/1953-0532$01.50/0 © 1988 American Chemical Society