An Approach to Systematization and Design of Organic Reactions

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Organic chemistry often looks like a colossal collection of an enormous variety of different reactions. The goal of chemists for more than a century was, and still is, to create a logical and rigorous system of organic reactions, possessing a predictive power. One of the earliest attempts in that direction was the type theory,[1a] whose main concept was that of "reaction formulas". Each of these formulas rationalized one of the possible transformations of an organic compound, and the existence of several reaction pathways led to a number of "rationale formulas". For example, the two formulas 1 and 2 for acetic acid[1] represented two different types of reactivity, namely, the acidic property (1) and substitution of the OH group (2). Thus, the classification of reaction types has been installed into formulas.

$$\left.\begin{array}{c} C_2H_3O \\ H \end{array}\right\}O \qquad C_2H_3O,OH$$

1   2

Today, "the basis of the science of organic chemistry is the structural theory. It is the basis upon which millions of facts about hundreds of thousands of ... compounds have been brought together and arranged in a systematic way."[2] The main tool of this theory is a structural formula, and the main theoretical concept

is a pairwise bond between atoms in a molecule.[3] This theory is very efficient in the construction of a system of organic compounds,[4] but a system of organic reactions is still far from perfect.

First, it should be clearly understood that a structural formula is not related to a reaction formula.[4] Therefore, in terms of that theory, reactions are described as an interconversion of starting systems into final ones, both of them being depicted by structural formulas. Second, there coexist many classifications of chemical processes which are not hierarchical and, therefore, cannot be used as a predictive tool for unknown reactions.

Many attempts have been made to construct an unambiguous system of organic reactions;[5] these systems are of different scope and limitations and vary in basic principles and in degrees of sophistication. Since 1975,

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(1) (a) Kekule, A. Lehrbuch der Organische Chemie oder Chemie der Kohlenstoffverbindungen; Enke Erlangen, 1859–1861; Band 1. (b) Accepting ^{12}C and ^{16}O.
(2) Morrison, R. T.; Boyd, R. N. Organic Chemistry, 4th ed.; Allyn and Bacon: Boston, MA, 1983; p 4.
(3) For a rigorous analysis of structural theory, see: Tatevskiy, V. M. The Classical Theory of Molecular Structure and Quantum Mechanics; Khimiya: Moscow, 1973 (in Russian).
(4) (a) Hückel, W. Theoretische Grundlagen der Organische Chemie; Akad-Verlag: Berlin, 1952; Band 1. (b) Zefirov, N. S.; Tratch, S. S.; Chizhov, O. S. Cage and Polycyclic Compounds. Molecular Design on Isomorphous Substitution Principle; Institut of Scientific Information: Moscow, 1979; Itogi Nauki Tekh., Ser: Org. Khim. (in Russian).
(5) Selected examples: (a) Mathieu, J.; Alliais, A.; Valls, J. Angew. Chem. 1960, 72, 71. (b) Balaban, A. T. J. Chem. Inf. Comput. Sci. 1985, 25, 334; Comput. Math. Appl. 1986, 12B, 999. (c) Hendrickson, J. B. Angew. Chem. 1974, 86, 71; J. Am. Chem. Soc. 1986, 108, 6748. (d) Sinanoglu, O. Ibid. 1975, 97, 2303. (e) Blair, J.; Gasteiger, J.; Gillespie, C.; Ugi, I. Tetrahedron 1974, 30, 1845. Bauer, J.; Rainer, M.; Fontain, E.; Ugi, I. Chimia 1985, 39, 43. Brandt, J.; Bauer, J.; Frank, R. M.; Scholley, A. Chem. Scr. 1981, 18, 53. Brandt, J.; Scholley, A.; Wochner, M. Phys. Commun. 1984, 33, 197. (f) Kvasnička, V. Collect. Czech. Chem. Commun. 1984, 4, 1090; 1985, 50, 1433.

Chart I
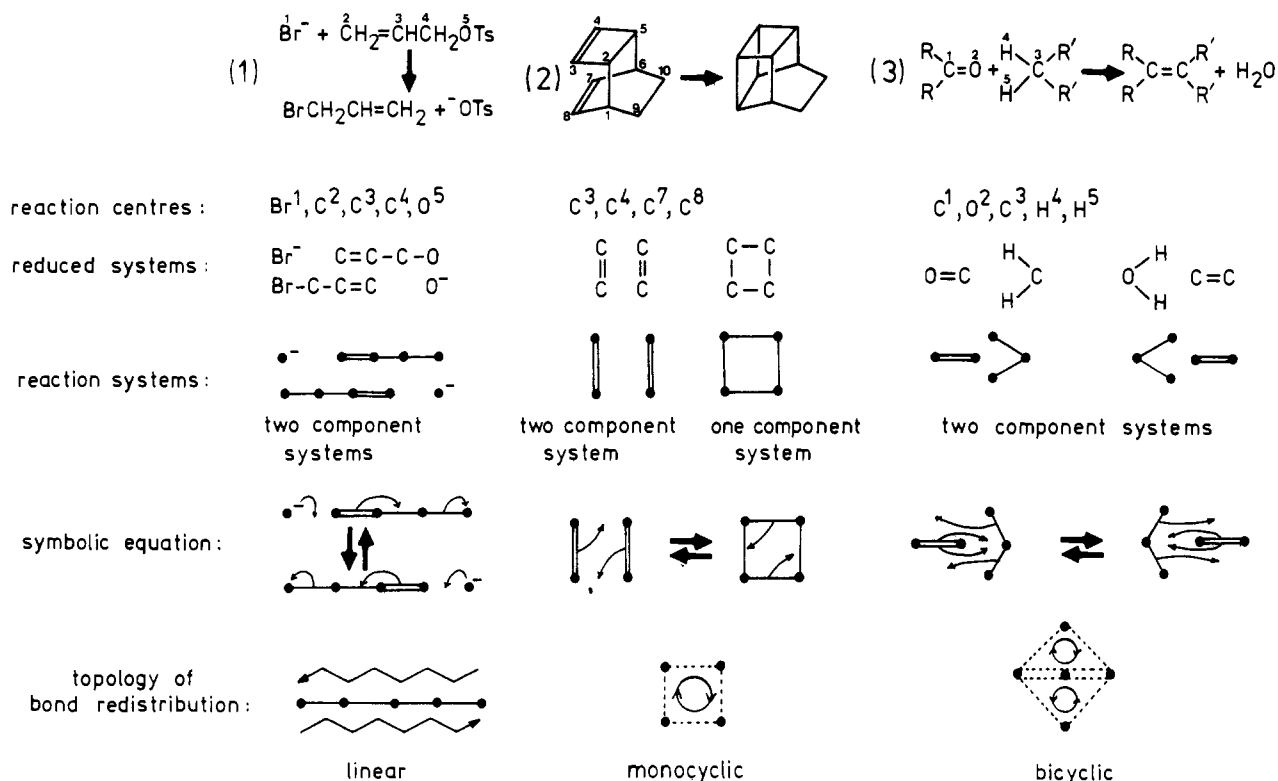
we have been developing a general formal–logical approach to organic reactions,[6–9] based on structural and graph theories, for the following purposes: (i) classification and systematization of chemical processes, (ii) methodology of a systematic search for new reactions (SYMBEQ[9d]), and (iii) elaboration of a logical basis for a system of computer programs for synthetic purposes (FLAMINGOES[7]). The goal of this Account is twofold: (i) to clarify the basic methodology of our approach in a less rigorous but more acceptable way and (ii) to demonstrate its potential for both the classification and the search for novel reactions.

To intrigue a reader, consider one simple problem. There are many [2+2]-cycloadditions, 3 → 4. One may pose the question, which *constitutional* characteristics must be incorporated into the component structures to secure the [1+3]-cycloadditions, 5 → 4? This and re-

lated problems can be easily solved by a formal–logical approach.
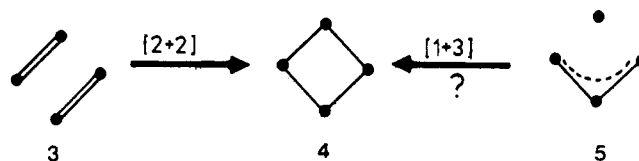
Basic Principles of a Formal–Logical Approach to Organic Reactions

Our approach is based entirely on structural theory. It ignores mechanisms or steps of the process and takes into account only the *overall* result, namely, the structures of the initial and final systems. The overall result is considered as a *bond redistribution* (BR) in the starting system to give the final system, as if this BR proceeds in a single step. Consider the classification procedure using as an example Chart I. First, one has to identify those atoms for which the number or the disposition of the bonds is changed. These atoms will be referred to as *reaction centers* (RC's). The complete set of reaction centers together with the complete set of changeable bonds (including "bonds" of zero order) forms *reaction systems*.

We define the *symbolic equation* (SEQ) as a specific record of a chemical equation using abstract symbols (heavy points in Chart I). The type of the contour formed by all changeable bonds[10] determines the *topology* of the bond redistribution. This contour can be represented by nonclosed lines, cycles, and, in principle, more complicated lines.[6f,g] Hence, chemical processes can be partitioned into those with linear,[8] monocycl-

(6) (a) Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.* **1975**, *11*, 225; (b) *Ibid.* **1975**, *11*, 1785; (c) *Ibid.* **1976**, *12*, 7; (d) *Ibid.* **1976**, *12*, 697; (e) *Chem. Scr.* **1980**, *15*, 4; (f) *Zh. Org. Khim.* **1982**, *18*, 1561; (g) *Ibid.* **1984**, *20*, 1121.

(7) (a) Tratch, S. S.; Zefirov, N. S.; Podymova, E. V. In *Proceedings of the 5th All-Union Conference on Application of Computers in Molecular Spectroscopy and Chemical Studies*; Theses: Novosibirsk, 1983; p 205. (b) Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.* **1981**, *17*, 2465. (c) Zefirov, N. S.; Tratch, S. S.; Gordeeva, E. V. In *Proceedings of the 7th All-Union Conference on Application of Computers in Molecular Spectroscopy and Chemical Studies*; Theses: Riga, 1986; p 19. (d) Gordeeva, E. V. Candidate Diss., Moscow, 1986.

(8) (a) Zefirov, N. S.; Tratch, S. S.; Gamziani, G. A. *Zh. Org. Khim.* **1986**, *22*, 1341. (b) Gamziani, G. A. Candidate Diss., Moscow, 1986.

(9) (a) Zhidkov, N. P.; Zefirov, N. S.; Popov, A. I.; Rodionov, A. V.; Tratch, S. S. In *Mathematical Problems of Structural Analysis and Algorithms of Computer Experiments in Organic Chemistry*; Zhidkov, N. P., Schchedrin, B. M., Eds.; Moscow State University: Moscow, 1979; pp 37, 59. (b) Tratch, S. S.; Zefirov, N. S. "Graph Automorphism Groups. Program Complex AUTOGRAPH"; see ref 7a, 1980, p 5. (c) Baskin, I. I.; Zefirov, N. S.; Tratch, S. S. *Zh. Org. Khim.*, accepted for publication. (d) Baskin, I. I.; Tratch, S. S.; Zefirov, N. S. "Program for Search of Novel Types of Reactivity of Organic Compounds (SYMBEQ)"; see ref 7c, 1986, p 88.

(10) Including the ones of zero order, e.g., $C_3...C_8$, in the starting system of reaction 2 of Chart I.
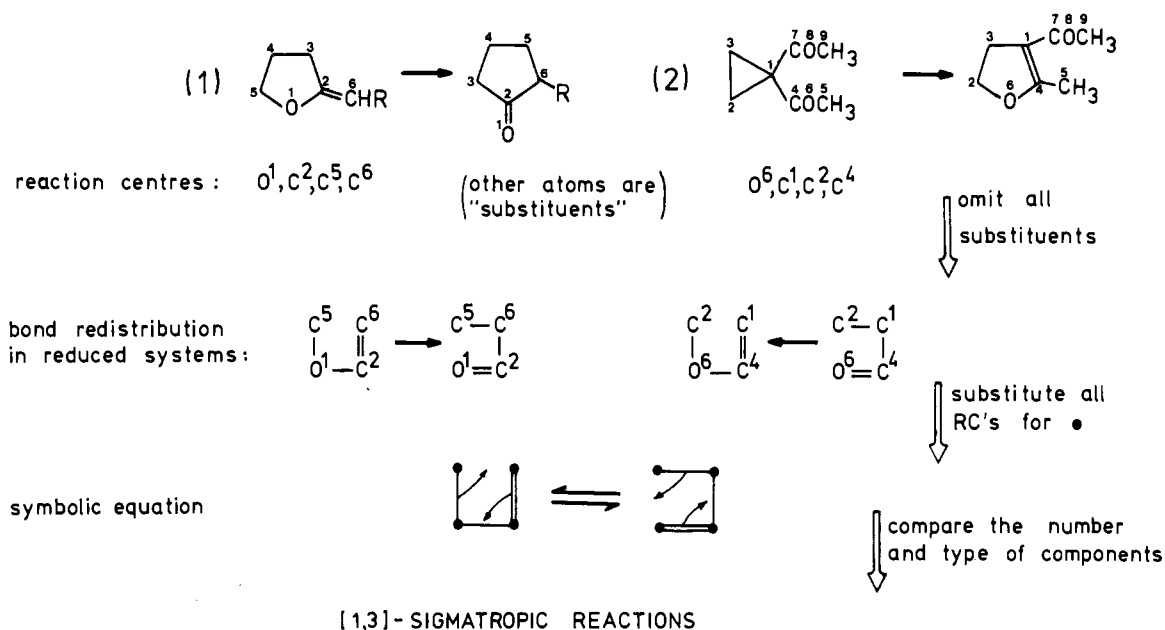
Chart II

(1) (structure) $\longrightarrow$ (structure)   (2) (structure) $\longrightarrow$ (structure)

reaction centres : O^1, C^2, C^5, C^6 (other atoms are "substituents") O^6, C^1, C^2, C^4

⇓ omit all substituents

bond redistribution in reduced systems:

$$\begin{array}{cc} C^5 & C^6 \\ | & \| \\ O^1 & C^2 \end{array} \longrightarrow \begin{array}{cc} C^5-C^6 \\ | & | \\ O^1=C^2 \end{array} \qquad \begin{array}{cc} C^2 & C^1 \\ | & \| \\ O^6 & C^4 \end{array} \longleftarrow \begin{array}{cc} C^2-C^1 \\ | & | \\ O^6=C^4 \end{array}$$

⇓ substitute all RC's for ●

symbolic equation   (graph) ⇌ (graph)

⇓ compare the number and type of components

[1,3] - SIGMATROPIC REACTIONS

Chart III

(1) $(C_6H_5)_2\overset{1}{C}H\overset{2}{O}\overset{3}{S}C_6H_5 \longrightarrow (C_6H_5)_2\overset{1}{C}H\overset{2}{\underset{||}{O}}\overset{3}{S}C_6H_5$ (2) $(CH_3)_2\overset{4}{A}s\overset{3}{S}\overset{2}{S}\overset{1}{A}s(CH_3)_2 \longrightarrow (CH_3)_2\overset{4}{A}s\overset{3}{S}\overset{2}{\underset{||}{S}}\overset{1}{A}s(CH_3)_2$

reaction centres: ordinary : $C^1\ O^2$ (other atoms are "substituents") $S^2\ S^3$
                     specific : S^3 As^1

⇓ omit all substituents

bond redistribution in reduced systems:

(structure) $\longrightarrow$ (structure)   (structure) $\longrightarrow$ (structure)

⇓ substitute ordinary RC's for ● and specific RC for X

symbolic equation :   (graph) ⇌ (graph)

⇓ compare the number and type of components

[1,2α] - [1,2β] - SIGMATROPIC REACTIONS
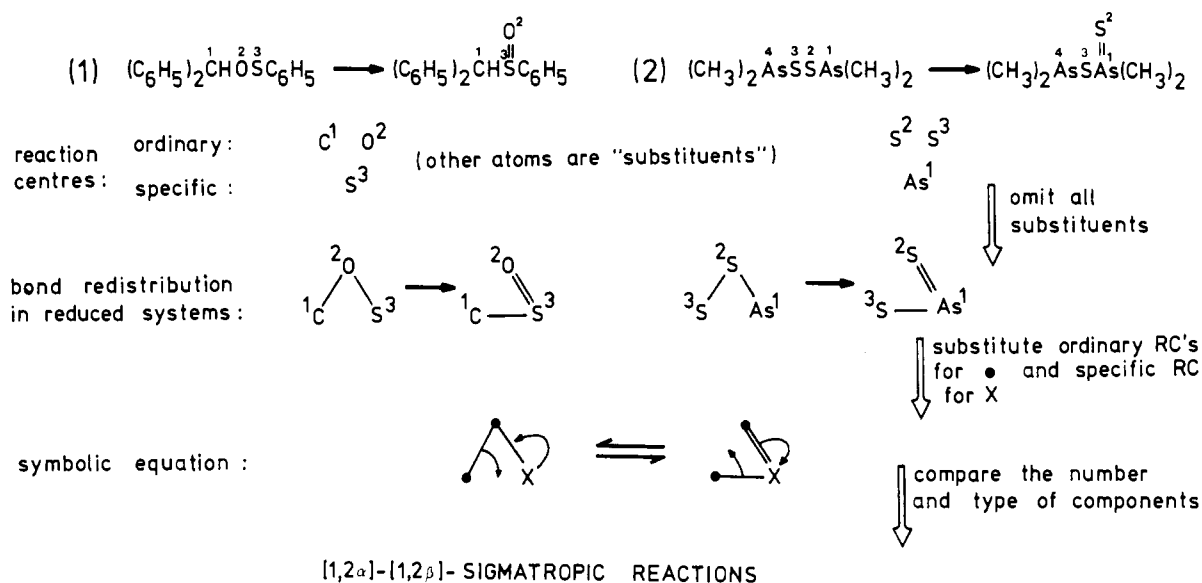
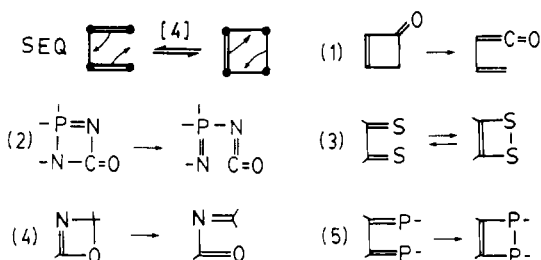ic,[6b–g,7] bicyclic,[6f,g] etc., topologies of bond redistribution.[11]

The most important topology is the *monocyclic* one (MT), for which a detailed classification of processes has been extensively and rigorously developed.[6–9] Charts II and III illustrate the classification procedure for four reactions, having monocyclic topology of bond redistribution. These examples reveal the presence of two different types of reaction centers (RC's): (i) those not changing their formal valence (ordinary RC's; denoted by heavy points) and (ii) those which change their valence number by two units (specific RC's; denoted by letters X, Y, etc.). It was shown that all possible re-

(11) Graph characterization of single-resonance structure and topology of BR depends on the resonance structure chosen.[6a–c,f] To eliminate ambiguity in the case of monocyclic topology, it is necessary to use noncharged, nonradical but covalent resonance structures irrespective of their actual participation in the resonance hybrid. In contrast, linear topology inevitably deals with BR in charged or radical structures.[8] The processes with bicyclic and other complex topologies can always be represented as a sequence of ones with linear and monocyclic topologies.[6f,g]

actions with monocyclic topology can be described in terms of ordinary and specific RC's if one uses noncharged and nonradical resonance structures.[6]

The following theorem was proven:[6a,g] the process with monocyclic topology at an even number of RC's requires an even number (0, 2, ...) of specific RC's; an odd number (1, 3, ...) of specific RC's must be necessarily involved in the system with an odd number of RC's. Chart III illustrates that statement. The four-centered processes with monocyclic topology can be performed either by using only ordinary RC's or by inserting two specific RC's into the structure of the reaction system. Now the first step to approach the [1+3]-cycloaddition problem can be made. Obviously, the isolated center in 5 must be a specific RC, because it became connected by two new bonds in 4. However, the three-centered framework must also contain one specific RC. This result is not trivial and can be reached by a general approach.

Chart IV

SEQ   [4]   (1)

(2) -P=N / -N-C=O → -P-N / -N C=O   (3)

(4) →   (5)

The Classification System of Organic Reactions with Monocyclic Topology of Bond Redistribution

For every process with monocyclic topology of bond redistribution, the reaction centers can be placed at the vertices of a regular polygon in such a manner that all bonds that change their order are situated on its edges. All other bonds must be unchanged. After the determination of the initial and final systems (e.g., Chart I), a further step consists in recognizing the types of interconversion of these reaction systems. Let us define a *component* as the set of those RC's which are connected by bonds of nonzero order, situated on the edges of the polygon. For processes with monocyclic topology the components must obviously have either a linear (Charts II and III) or a cyclic (final system of eq 2 of Chart I) structure. In turn, reaction systems can be constructed either from one component (linear or cyclic) or from several components, necessarily of linear structure. Thus, the only possible types of reactions with monocyclic topology are (1) ring ⇌ chain transformations or electrocyclic reactions, (2) chain ⇌ chain transformations or sigmatropic reactions, (3) ring ⇌ ring transformations or resonance of nonpolar structures, (4) one-ring ⇌ several-chain transformations or cycloaddition–cyclofragmentation reactions, (5) one-chain ⇌ several-chain transformations or addition-elimination reactions, and (6) several-chain ⇌ several-chain transformations or "cyclodismutation" reactions (see Table I). We must emphasize that *these six types completely cover the classification of reactions with monocyclic topology.*[6,7]

Every type of interconversion can be represented by a definite number of symbolic equations (SEQ's).[6b,c,e,7a] Indeed, SEQ's are the main tool of our approach, and its main advantage is the possibility of deriving complete sets of SEQ's,[6b,c,7a,8] which have been in part tabulated.[6c,8b] The numbers of SEQ's are listed in Table I.[12] For instance, there exist two SEQ's for [1 + 3]-cycloaddition,[6c] 5 → 4.

Exemplification of the Classification System of Organic Reactions with Monocyclic Topology of Bond Redistribution

The finite set of symbolic equations (Table I) forms the framework for the exhaustive description of the processes with monocyclic topology. The goal of this section is to clarify the classificational application of

(12) A rigorous treatment can be also achieved by introducing the notion of reaction fragments and classificational equations,[6b,g] which permits one to elaborate the unambiguous system of designation of SEQ's.[6b,c,g] Briefly, it is based on the generally accepted [i+j] or [i,j] notations. The position of specific RC's is labeled by a Greek letter (e.g., Chart III; please notice the double notation, one for direct and one for reverse processes). The resulting uniform notation system completely covers all types of BR with MT (for examples see Table I).
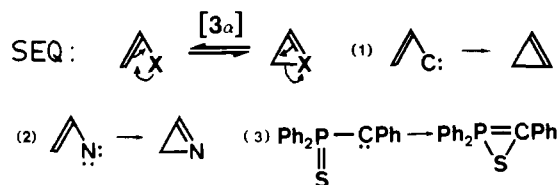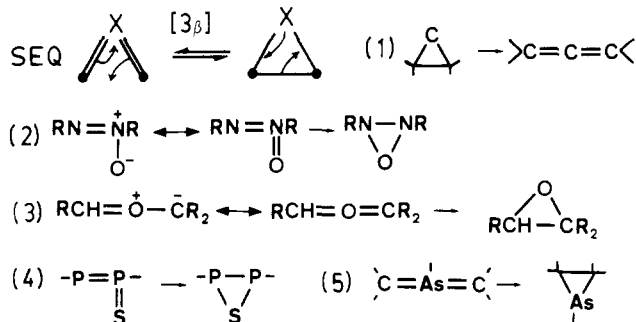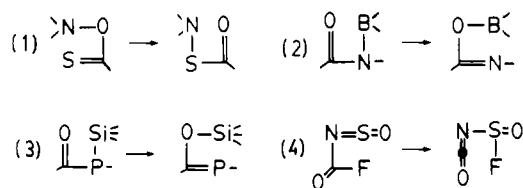
Chart V

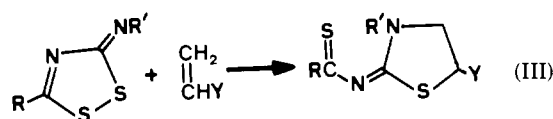SEQ: [3a]   (1)

(2)   (3) Ph₂P—CPh → Ph₂P=CPh

Chart VI

SEQ   [3β]   (1)   → >C=C=C<

(2) RN=N⁺R ↔ RN=NR → RN—NR

(3) RCH=Ȯ—C̄R₂ ↔ RCH=O=CR₂ → RCH—CR₂

(4) -P=P- / S → -P—P- / S   (5) C=As=C —

Chart VII

(1) >N—O / S → >N O / S   (2) O B< / N- → O—B< / N-

(3) O Si≡ / P- → O—Si≡ / P-   (4) N=S=O → N—S=O
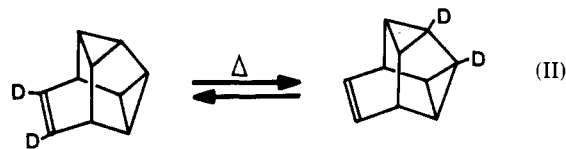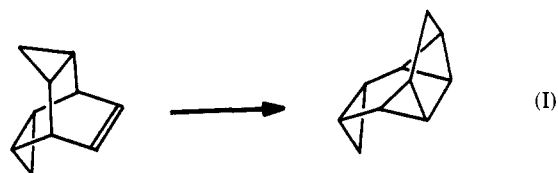
the approach. Before proceeding further we ask a reader to classify reactions I–III in his own way.

(I)

(II)

(III)

Electrocyclic Reactions (ER). In our terms electrocyclic reactions are defined as transformations of a one-component linear system into a one-component cyclic one, or vice versa (Table I). The classical example of [4]-ER[12] is shown in Chart IV; the symbolic equation of [4αγ]-ER is shown in Table I. There exist three three-centered electrocyclic reactions (Table I), two of them with one specific reaction center: [3α] (Chart V) and [3β] (Chart VI).[13] For more examples, especially tautomerism, see ref 6d,e.

Sigmatropic Reactions (SR). Chart III shows the single possible symbolic equation of a three-centered
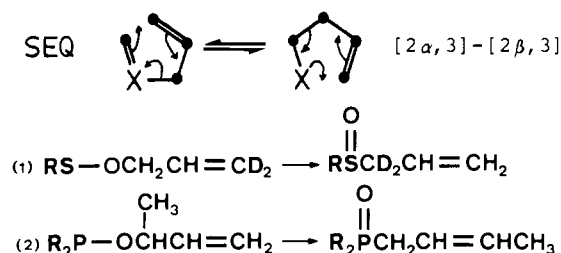
(13) We considered only nonpolar resonance structures.[11]

Table I.
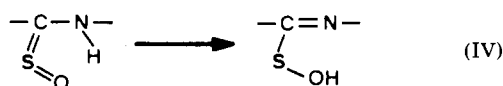**Classification of Reactions with Monocyclic Topology of Bond Redistribution**

The type (subtype) of process	Schematic picture	The number of SEQ's[a] number of RC's				Example of SEQ and its designation
		3	4	5	6	
Interconversions of the one-component systems						
1. Electrocyclic reactions		3	6	10	20	[4αγ]
2. Sigmatropic reactions		1	5	8	25	[1,4γ]-[1,4β]
3. Ring-ring interconversions or resonance of non-polar structures		2	4	4	8	
Interconversions of the multi-component systems						
4. Cycloaddition and cyclo-fragmentation (including oligo-subclass)		3	9	21	59	[2+4]
5. Addition and elimination reactions		1	5	19	73	[2+(1,1)]
(a) [1,n]-addition (elimination)		1	2	3	6	[1+2+(1,1)]
(b) oligoaddition (oligo-fragmentation)		0	1	3	12	
(c) sigmatropic addition (elimination)		0	2	11	38	[2+(1,2α)]
(d) sigmatropic oligoaddition (oligofragmentation)		0	0	2	17	[1+1+(1,2α)]
6. Cyclodismutation reactions		0	2	6	41	[1,1)+(1,1)]

[a] The numbers of SEQ's have been calculated accepting a participation up to a maximal number of specific reaction centers. The SEQ's tabulated in ref 9 have not more than three specific RC's.
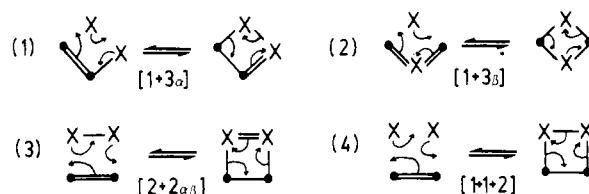
Chart VIII

SEQ [2α,3]-[2β,3]

(1) $RS-OCH_2CH=CD_2 \longrightarrow RSCD_2CH=CH_2$

(2) $R_2P-OCHCH=CH_2 \longrightarrow R_2PCH_2CH=CHCH_3$ (with CH_3 substituent and O)

sigmatropic reaction.[12] Chart II shows the [1,3]-SR at four centers.[6d,e] We illustrate this type with less trivial variants (Chart VII). The other four symbolic equations for four-centered sigmatropic reactions are depicted and discussed elsewhere.[6] The SEQ's for two of the three possible five-centered sigmatropic reactions are shown in Table I and Chart VIII. It is of interest that sulfenate–sulfoxide rearrangement (1 in Chart VIII) has been independently found in four laboratories[14] starting from different ideas; we have used this approach as a guide concept.[14d] The SEQ of the five-centered sigmatropic reaction of Table I can be represented by reaction IV.
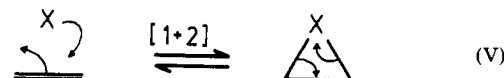

(IV)

Chart IX

(1) [1+3α] (2) [1+3β]

(3) [2+2αβ] (4) [1+1+2]

Ring–Ring Interconversions. This approach considers resonance structures as different reaction systems.[11] This type describes firstly the resonance of canonical forms (e.g., of Kekule's structures).[15] Second, it describes rare cases of ring–ring rearrangements, such as that for cyclobutadienes[16] (Table I) and cyclooctatetraenes.[17]

Cycloaddition–Cyclofragmentation[18] Reactions (CCR). [1+2]-CCR (eq V) represents many well-known additions of carbenes and their analogues to a double bond. The symbolic equations of well-known [2+2]-CCR (Chart I) also has many realizations, including such bonds as C=O, C=N, C=S, C=P, P=N, P=S, P=P, and Si=S.

[1+2] (V)

(14) (a) Miller, E. G.; Rainer, D. E.; Thomas, H. T.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4861; **1966**, *88*, 3138. (b) Braverman, S.; Stabinsky, J. *Isr. J. Chem.* **1967**, *5*, 125; **1967**, *5A*, 71. (c) Abbott, D. J.; Stirling, C. M. *Chem. Commun.* **1968**, 165. (d) Zefirov, N. S.; Abdulvaleeva, F. A. *Vestn. Mosk. Univ., Ser. 2: Khim.* **1969**, 135; **1970**, 725. *Zh. Org. Khim.* **1971**, *7*, 947.
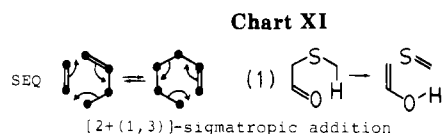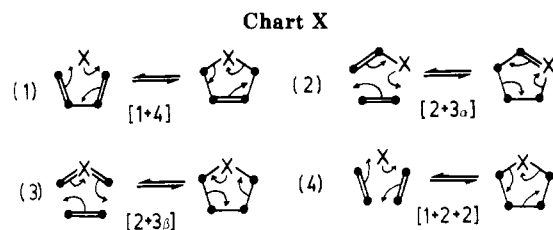
(15) Remember also the familiar resonance of nonpolar canonical forms of thiophene with sulfur as a specific RC.

(16) Whitman, D. W.; Carpenter, B. K. *J. Am. Chem. Soc.* **1982**, *104*, 6473. Ming-Ju Huang; Wolfsberg, M. *Ibid.* **1984**, *104*, 4039.
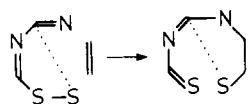
(17) Paquette, L. A.; Trova, M. P. *Tetrahedron Lett.* **1986**, *27*, 1895 and references therein.

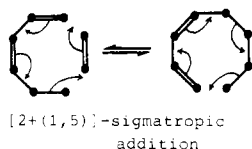(18) We prefer this term instead of the occasionally used terms "cycloelimination" and "cycloreversion".

Chart X

(1) ... [1+4]   (2) ... [2+3a]

(3) ... [2+3β]   (4) ... [1+2+2]

Chart XI

SEQ ... [2+(1,3)]-sigmatropic addition

(1) ...

classification of the reaction 8 :

a) reduced systems: b) SEQ :

... [2+(1,5)]-sigmatropic addition

We are ready now to turn to [1+3]-CCR. Chart IX exhibits all possible symbolic equations of four-centered cycloaddition–cyclofragmentation reactions with two specific reaction centers. The SEQ's 1 and 2 of Chart IX can be considered as [1+3]-CCR. The real example of [1+3β]-cycloaddition is presented by reaction VI.[19]

$$C_6H_5CH = N = C(COOCH_3)_2$$
$$+$$
$$R—N=C$$
$$\longrightarrow$$

(VI)
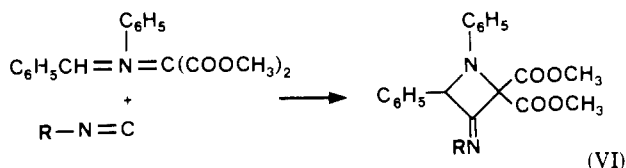
Four possible SEQ's for five-centered processes with one specific reaction center are shown in Chart X. The first one represents the so-called "chelatropic" reactions, and the two others embrace Huisgen's "1,3-dipolar cyclo-additions". The fourth is a five-centered oligo-CCR.

Addition–Elimination Reactions (AER). An addition means that one linear component becomes split into two fragments, both of which add to the ends of another linear component (Table I). Hence, the designation[12] of that type should be [n+(i,j)]. The first subclass is the addition of a two-centered component, i.e., [n+(1,1)]-AER's. The most typical SEQ is [2+(1,1)]-AER (Table I). The above-mentioned interconversion (eq I) is also a [2+(1,1)]-AER: it consists of the addition of a C—C bond to a C=C bond.

The second subclass is the addition of a linear component which contains three or more RC's (i + j ≥ 3). This process includes sigmatropic splitting of this component; hence, we have suggested the term "*sigmatropic addition*" to name this subclass (Table I). The SEQ of [2+(1,3)]-sigmatropic addition is shown in Chart XI. Some of the examples of this process are, in fact, very familiar, including ene reactions and decarboxylations of β-keto esters. A less known case is examplified in Chart XI by eq 1.[20] Reaction III[21] is an example of a [2+(1,5)]-sigmatropic addition (Chart XI).

(19) Deyrup, J. A. *Tetrahedron Lett.* **1971**, 2191. Burger, K.; Mann, F.; Brown, A. *Synthesis* **1975**, 250. Charrier, J.; Foucaud, A.; Person, H.; Loukauon, E. *J. Org. Chem.* **1983**, *48*, 482.

(20) Vedejs, E.; Perry, D. A. *J. Org. Chem.* **1984**, *49*, 573.

(21) For a review, see: Drozd, V. N.; Zefirov, N. S. *Sulfur Rep.* **1984**, *1*, 271.

Cyclodismutation Reactions. These SEQ's are quite numerous. The simplest SEQ, that of [(1,1)+(1,1)]-cyclodismutation, is shown in Table I. The particular case of this SEQ containing one nonreacting diagonal bond has been termed in the literature a "diotropic" rearrangement[22] (cf. ref 6d,e). Reaction II is an example of [2+(1,2,1)]-cyclodismutation, expressed by SEQ VII.

(VII)
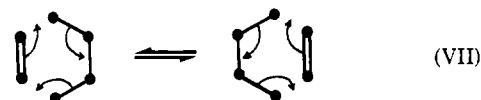
The Formal–Logical Approach as a Tool in the Search for New Reactions

Structural analogy at different levels of sophistication has been and still is a main tool of organic chemists for designing novel reactions. A more indirect analogy is more appreciated by chemists. The symbolic equations reflect fundamental information of possible structural changes in the course of organic reactions and hence permit one to develop the analogy up to the exhaustive computer level. In other words, SEQ's contain hidden information about great numbers of analogous reactions (e.g., Charts IV–VI and VIII), which permit their use in a reverse sense, namely, as a basis for the systematic examination of, and search for, new organic reactions.

The simplest way is to take a SEQ, for which a number of real processes have been previously found, and to create another chemical process by introducing symbols of chemical elements in place of RC symbols (e.g., Charts II and III). For instance, the known cases of [2+2]-cycloaddition (Chart I) or [1,3]-sigmatropic rearrangements (Charts II and VII) may be easily supplemented with a variety of analogous reactions. In place of specific RC's one has to introduce those elements which are capable of changing their formal valency by two units, e.g., $N^{3+} \rightleftarrows N^{5+}$, $P^{3+} \rightleftarrows P^{5+}$, $S^{2+} \rightleftarrows S^{4+}$, $S^{4+} \rightleftarrows S^{6+}$. Creative results may be obtained with a carbon atom as a specific RC, $C^{2+} \rightleftarrows C^{4+}$. Thus, pure combinatorial operations can create many instructive novel suggestions for finding novel reactions from every SEQ (e.g., Chart VIII).

An especially valuable procedure is to construct reduced chemical equations (Charts II and III) from those SEQ's which have no reported examples and hence to discover a novel topological type of chemical process. For instance, [2,2]-sigmatropic rearrangements[6d,e] or [1+3α]-cycloadditions are good candidates for these still unknown cases of bond redistribution to be discovered.

Development and Other Applications of the Approach

We have convincingly demonstrated the usefulness of systematic analysis of sets of SEQ's. The benefit of the approach is the accessibility of complete sets of SEQ's for bond redistribution with monocyclic topology. The generation and classification of SEQ's for processes with linear topology (including charged and radical systems) have also been performed.[8] Let us pose a question: Is it possible to construct complete sets of SEQ's for any given topology of bond redistribution? To answer, one needs to address graph, group, and combinatorial-object theories. The rigorous mathe-

(22) The term suggested in: Reetz, M. T. *Tetrahedron* **1973**, *29*, 2189.

matical statement of the problem (based on the Pòlya-de Bruijn model[23]) was discussed elsewhere.[7a,9,24] To date, the algorithms for generation of SEQ's are verified and the appropriate computer programs are written (ELSE,[8] SYMBEQ[9]). Thus, we can now create and graphically output the complete sets of SEQ's for every given topology.[25,26]

Conclusion

The formal–logical approach is an a priori formulation of necessary structural requirements incorporated into structures of reactants to perform a bond redistribution of a particular type. Such a treatment can be accomplished in a rigorous way to obtain, and what is more, to constructively enumerate complete sets of SEQ's for every topology of bond redistribution. The introduction of element symbols instead of reaction center symbols enables them to be used as the instrument in the search for new reactions. This approach also represents an extensive and rigorous classification system of organic reactions, which may be used for information storage.

Of course, the depth of one's penetration into any problem will never exceed the limit of the theory used. This approach is based on the structural theory; moreover, it is the next step in the development of structural theory up to the computerized form. Thus, it may give as much as that theory may provide. In all applications of structural theory to problems of reactivity, one may pose a question (i.e., write a proposed reaction),[3,4] but only experiment can judge the reality of its performance.

To predict the course of a chemical reaction, one needs to supplement the structural basis with a knowledge of thermodynamics, kinetics, mechanisms, MO considerations, stereochemical demands, etc. Only an "alloy" of different branches of present theories will be the framework of the future theory of organic reactions.

(23) Faradzhev, I. A. In *Algorithmic Studies in Combinatorics*; Nauka: Moscow, 1978; p 3 (in Russian).

(24) (a) Generation of SEQ's needs in some cases an algorithmization of a special subgroup of generalized wreath product.[24b] (b) Zefirov, N. S.; Kaluzhnin, L. A.; Tratch, S. S. In *Algebraic Theories of Combinatorial Objects*; Faradzhev, I. A., Klin, M. H., Eds.; VINITI: Moscow, 1985; p 175 (in Russian).

(25) This approach was also used for a description of mechanisms of organic reactions.[9c]

(26) This approach was successfully used as logical basis of the program for nonempirical computer-assisted synthesis (FLAMINGOES).[7]

# Acyclic Stereocontrol via Allylic Organometallic Compounds

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Acyclic stereocontrol is a pressing concern in modern organic chemistry,[1] and a number of methods have been developed for the stereoregulated synthesis of conformationally nonrigid complex molecules, such as macrolide and polyether antibiotics.[1] Special attention has been paid to aldol reactions, which constitute one of the fundamental bond constructions in biosynthesis. The reaction of allylic organometallic reagents (1) with aldehydes is synthetically analogous to the aldol addition of metal enolates (2),[2] since the resulting homoallyl alcohol (3) can be easily converted to the aldol (4).[3] Further, the allylmetal additions have significant advantages over aldol condensations, since the alkenes may be readily transformed into aldehydes (5),[2] may undergo a facile one-carbon homologation to δ-lactones (6) via hydroformylation,[4] or may be selectively epoxidized to introduce a third chiral center (7).[5] Nowadays, the allylic organometallic method has become

Scheme I
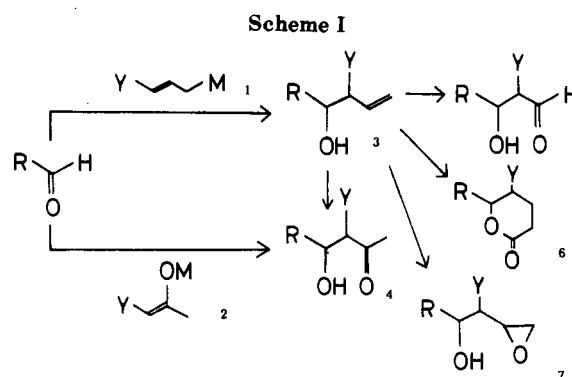
one of the most useful procedures for controlling the stereochemistry in acyclic systems.

(1) Reviews: (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203. (d) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (e) MaGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. (f) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (g) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. (h) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

(2) (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.