Organic Reaction Schemes and General Reaction – Matrix Types, I
Rearrangement Reactions

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Reaction-matrices, Rearrangement Reactions

A sample consisting of about 120 organic rearrangement reactions has been quantified in terms general reaction matrices $\tilde{R}$ expressing electron-flow processes. About two thirds of the reactions considered conform to only two distinct $\tilde{R}$-matrices, 80% to five such schemes. The frequency distribution is qualitatively similar to that found for larger, more randomly chosen, sets of organic reactions. Examples of the various electron-flow processes are given. The bearings of the results on synthesis-planning are discussed.

1. Introduction

Recently, Ugi and coworkers[1–6] have laid the basis of a mathematical model of chemistry, with the primary object of application to computer-assisted design of syntheses. According to this scheme, algebraic structures represent chemical systems and chemical reactions are described as isomerizations of ensembles of starting materials EM_A into a target molecule and by-products, EM_Z. As bond-electron (BE) matrices were chosen for the computer representation of an EM, a chemical reaction, corresponding to the transformation of one BE-matrix into another, $\tilde{E}_A \rightarrow \tilde{E}_Z$, is effectively expressed by addition of a *reaction matrix* $\tilde{R}$, *i.e.* $\tilde{E}_A + \tilde{R} = \tilde{E}_Z$. On the basis of the definition of a BE matrix $\tilde{E}$ for an *n*-atomic ensemble of molecules as an $n \times n$ matrix with e_{ij} entries corresponding to the formal covalent bond order between the atoms A_i and A_j, and e_{ii} to the number of free electrons of atom A_i, it follows that the entries $r_{ij} = r_{ji}$ of $\tilde{R}$ express bond breaking and formation processes, with r_{ii} accounting for changes in the distribution of free electrons. In short, an $\tilde{R}$-matrix is then an algebraic expression describing the electron-flow process of an individual chemical transformation of some concrete ensemble of starting molecules into a resulting concrete ensemble of product molecules. On the basis of a semi-empirical analysis of processes involving rupture of one, two and three bonds, it has been claimed[7] that such "individual" reaction matrices (describing individual, *i.e.* concrete organic reactions) may be classified into a limited number of groups called "general $\tilde{R}$-matrix types," each such type being described by structural *reaction schemes* very much like the ordinary structural schemes often used by organic chemists for the representation of reaction types.

We have now taken up the matter with the object of independently investigating this restricted set of reaction types and to classify organic chemistry accordingly. In this paper, in particular, we are concerned with organic rearrangement reactions. The choice of the subject matter is not casual. Rearrangements, by their intriguing nature, have arisen more than average attention in organic chemistry, which is usually the chemistry of functional groups. The selection of 120 reaction types considered, although being quite representative for the whole set of rearrangement reactions, is obviously only a subset of all organic reaction types described in the literature.

With regard to nomenclature, we notice that the electron flow of an organic reaction may be expressed either in the form of a "reaction matrix" (see above) or as a "reaction scheme"; due to the biunivocal relation between these representations[1], we deliberately use both terms in this and following papers. Typical examples of reaction schemes are to be found in Tables I–III and are referred to as being of $\tilde{R}n$ matrix type, where *n* is an arbitrarily chosen ordering number.

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Table I. Organic rearrangement reaction of the type $A{-}B + C{-}D \rightarrow A{-}C + B{-}D$ (R 1).

1. Rearrangement of substituted ethylene oxides.
2. Alkyl shifts in non-cyclic compounds.
3. Wagner-Meerwein rearrangement (1,2 shift in bicyclic system).
4. Rearrangement of peroxyderivatives.
5. Rearrangement of hydroperoxide esters.
6. Wittig rearrangement.
7. Truce-Smiles rearrangement.
8. Enol-keto tautomerism.
9. Keto-cyclol tautomerism (ring-chain tautomerism).
10. Keto-lactol tautomerism (intramolecular semiacetal formation).
11. Intramolecular Michael reaction.
12. Prototropic change (mobile hydrogen tautomerism).
13. Prototropic shifts in allylic systems.
14. Anionotropic change (S_N1' and S_N2').
15. Intra-annular valency tautomerism.
16. Orton rearrangement.
17. Rearrangement of diazoaminobenzenes.
18. Fisher-Hepp rearrangement.
19. Hofmann-Martius rearrangement.
20. Reilly-Hickinbottom rearrangement.
21. Rearrangement of N-nitroaniline.
22. Rearrangement of alkyl aryl ethers.
23. Fries rearrangement of aryl esters to acylphenols.
24. Benzidine rearrangement.
25. Claisen rearrangement without allyl reversal.
26. Rearrangement of hydroxylamines.
27. Rearrangement of nitroamines.
28. Three-carbon allylic transformations (allylic halides, esters, alcohols).
29. Ring-chain anionotropy.
30. Ring closures of cyclohexenylethyl and cycloheptenylcarbinyl derivatives.
31. Ring expansions of norbornylcarbinylderivatives.
32. Thermal and acid-catalyzed rearrangements of cyclopropane and -butane derivatives.
33. Demjanov rearrangement.
34. Wessely-Moser rearrangement.
35. Amadori rearrangement.
36. Dimroth rearrangement.
37. Hayashi rearrangement.
38. Rowe rearrangement.
39. Wallach rearrangement.
40. Theilacker rearrangement.
41. Chapman rearrangement.
42. D-Homo rearrangement.
43. Nierenstein reaction (2° step).
44. Baker-Venkataraman transformation.
45. Bardhan-Sengupta phenanthrene synthesis (1st step).
46. Darzens synthesis of tetralin derivatives.
47. Dieckmann reaction.
48. Barton reaction (2* $\tilde{R}$ 1).
49. Beckmann rearrangement (2* $\tilde{R}$ 1).
50. Meyer-Schuster rearrangement (2* $\tilde{R}$ 1).
51. Rupe rearrangement (3* $\tilde{R}$ 1).

Table II. Organic rearrangement reactions of the type $A{-}B + C{-}D + E{-}F \rightarrow A{-}C + D{-}E + B{-}F$ ($\tilde{R}$ 2).

1. Pinacol-pinacolone rearrangement/retropinacolic change.
2. Conversion of (α-hydroxy) aldehydes and -ketones (pinacolic type transformation)*.
3. Acyloin rearrangement.
4. Benzil-benzilic acid conversion.
5. Halohydrin rearrangement.
6. Semipinacolic deamination.
7. Nametkin rearrangement.
8. Molecular rearrangement by neighbouring group partecipation in substitution reactions.
9. Transannular rearrangements.
10. Anionotropic change (S_Ni').
11. Claisen rearrangement (with allyl reversal) and analogs.
12. Cope rearrangement.
13. Rearrangements in conjugated triene systems.
14. Intra-annular valency tautomerism.
15. (Rearrangement of diazo-amino-compounds)**.
16. (Fischer-Hepp rearrangement)**.
17. Benzidine rearrangement.
18. Rearrangement of ketene acetal.
19. Five-carbon allylic shift.
20. Thermal rearrangement of cyclopropane and -butane derivatives.
21. 1,2 Rearrangement during Clemmensen reduction.
22. Bogert-Cook synthesis.
23. Favorskii rearrangement.
24. Westphalen-Lettré rearrangement.
25. Perkin rearrangement (coumarin-benzofuran ring contraction).
26. Ciamician-Dennstedt rearrangement (2nd step).
27. Lobry de Bruyn–van Ekenstein transformation.
28. Reverdin migration.

* On the basis of an intramolecular reaction mechanism.

** On the basis of an intermolecular reaction mechanism.

Table III. General reaction matrix types of organic rearrangements.

$\tilde{R}$ 1 $A{-}B + C{-}D \rightarrow A{-}C + B{-}D$

See Table I.

$\tilde{R}$ 2 $A{-}B + C{-}D + E{-}F \rightarrow A{-}C + D{-}E + B{-}F$

See Table II.

$\tilde{R}$ 3 $A{-}B + C{-}D \rightarrow A + B{-}C + D$:

1. Rearrangement of peroxyderivatives.

$\tilde{R}$ 4 $A{-}B + C{=}D{-}E{-}F \rightarrow A{-}\underset{\substack{|\\ F}}{D}{-}B + C{=}E$

1. Neber rearrangement (α-aminoketones from ketoximes).

$\tilde{R}$ 5 $A{-}B + {:}C{-}D \rightarrow A{-}C{-}B + D$:

1. Wolff rearrangement (fundamental step).
2. Curtius rearrangement[22].
3. Schmidt rearrangement[23].
4. Azide rearrangement.
5. Bamford-Stevens reaction (last step).

$\tilde{R}$ 6 $A{-}B{-}C{-}D{-}E \rightarrow A{-}C{-}E + B{=}D$

1. Beckmann rearrangement.

2. Procedures

Instead of setting up the $\tilde{R}$ matrices corresponding to organic reactions, we rather consider here the relevant reaction schemes. In particular, these are

Table III continued

$\tilde{R}$ 7 $A{-}B + C{-}D{-}E \rightarrow A{-}D{-}B + C{-}E$
1. Hofmann rearrangement[24].
2. Lossen rearrangement[25].
3. Stieglitz rearrangement of hydroxylamines.
4. Haloamine rearrangement.
5. Fritsch-Buttenberg-Wiechell rearrangement.

$\tilde{R}$ 8 $A{-}B + C{-}D + E{:} \rightarrow A{-}C + D{-}E + B{:}$
1. Sommelet rearrangement.
2. Grob's fragmentation of γ-aminohalides and α-aminoketoximes[26].

$\tilde{R}$ 9 $A{-}B + C{-}D{-}E \rightarrow A{-}E + B{-}C + D{:}$
1. Transformations in allylic alcohol derivatives. (S_Ni' rearrangement of chlorosulfites and -formates).
2. Acetylene-allene rearrangements.

$\tilde{R}$ 10 $A{-}B{-}C + D{=}E \rightarrow A{-}D{-}C + B{=}E$
1. Meyer-Schuster rearrangement (Cfr. $\tilde{R}$ 1).
2. Tiemann rearrangement, 3rd step (RNHCN→ RNHCONH$_2$)
3. Curtius rearrangement
4. Hofmann rearrangement } last step (RNCO→RNH$_2$)
5. Lossen rearrangement

$\tilde{R}$ 11 $A{-}B + C \rightarrow A{-}C + B$
1. Migration of alkyl groups during the Fischer Indole Synthesis.

$\tilde{R}$ 12 $A{:} + B{-}C \rightarrow A{-}C + B{:}$
1. Stevens rearrangement
2. Grovenstein-Zimmerman rearrangement.
3. Meisenheimer rearrangement.

$\tilde{R}$ 13 $A{-}B{-}C + D{-}E + F{:} \rightarrow A{-}D + C{-}E + {:}B{-}F$
1. Weerman degradation.

$\tilde{R}$ 14 $A{-}B{-}C{-}D{:} \rightarrow A{-}C{:} + B{=}D$
1. Rearrangement of nitrones.

$\tilde{R}$ 15 $A{-}B + C{-}D + {:}E{-}F \rightarrow A{-}E{-}D + B{-}C + F{:}$
1. Schmidt reaction (azidohydrin rearrangement).
2. Darapsky degradation (overall rearrangement step).

$\tilde{R}$ 16 $A{-}B{-}C + D{-}E{-}F \rightarrow A{-}C + B{=}E + D{-}F$
1. Tiemann rearrangement of amidoximes (overall).

$\tilde{R}$ 17 $A{-}B + C{-}D + E{-}F + G{-}H \rightarrow$
$A{-}D + B{-}H + C{-}E + F{-}G$
1. Rearrangement involving eight atomic centers.

$\tilde{R}$ 18 $A{-}B + C{-}D + E{-}F{-}G \rightarrow A{-}G + B{-}E + D{-}F{-}C$
1. Dienol-benzene rearrangement.
2. Dienone-phenol rearrangement.

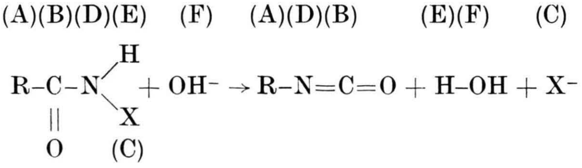
$\tilde{R}$ 19 $A{-}B + C{-}D{-}E + F{-}G{-}H \rightarrow$
$A{-}H + B{-}E + F{-}C + G{=}D$
1. Gabriel-Colman rearrangement.

$\tilde{R}$ 20 $A + B{-}C{-}D \rightarrow A{-}C + B{-}D$
1. Wallach degradation of α,α'-dihaloketones.

derived for (a) heterolytic rearrangements in reactions of isomerization, substitution, or elimination undergone by saturated all-carbon, carbon-nitrogen, and carbon-oxygen systems, involving a shift of a group carrying an excess of electrons to an electron-deficient centre or its polar opposite (nucleophilic and electrophilic rearrangements, respectively), (b) unsaturated rearrangements, (c) aromatic electrophilic, nucleophilic and intramolecular rearrangements, and (d) molecular reactions. In general, the overall reactions considered involve only one or two molecular species. In view of the object of our study, namely the derivation of a set of $\tilde{R}$-matrices for use in synthesis-planning and classification and codification of organic reactions (cfr. Vléduts[8]), we normally proceed by considering the generalized overall expression of the chemical rearrangement step, without going into finer details of mechanism, unless specifically required.

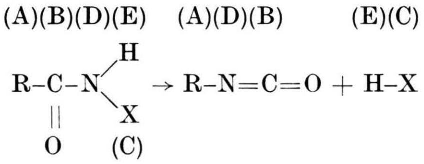
Some ambiguity in the classification of organic reactions may be inavoidable as long as reaction mechanistic aspects are obscure. In case of non-concerted mechanisms, when possible the rearrangement steps have been separated from other processes. Therefore, in this paper we do not normally take into account any preliminary steps, such as the condensation of carboxylic acid and hydrazoic acid to give acylazide in the Schmidt reaction or the formation of a N-haloamide in the Hofmann reaction, and neither subsequent decomposition of the rearrangement products. We thus describe processes which account for the fundamental steps only, avoiding however those intermediates which would represent unstable products in a synthesis-tree, and other processes which may be considered to give rise to independent nodes.

A typical case of setting up reaction schemes is illustrated in the following example, referring to the Hofmann rearrangement of N-haloamides to isocyanates in basic solutions:



$$R{-}\underset{\underset{O}{\|}}{C}{-}N\begin{smallmatrix}H\\X\end{smallmatrix} + OH^- \rightarrow R{-}N{=}C{=}O + H{-}OH + X^-$$

(Reaction scheme:
$A{-}B + C{-}D{-}E + F{:} \rightarrow A{-}D{-}B + E{-}F + C{:}$)
which might also be written as:



$$\overset{(A)(B)(D)(E)}{\underset{\underset{O}{\|}}{R\text{–}C}\text{–}N\begin{smallmatrix}\diagup H\\ \diagdown X\\ (C)\end{smallmatrix}} \rightarrow \overset{(A)(D)(B)}{R\text{–}N{=}C{=}O} + \overset{(E)(C)}{H\text{–}X}$$

(Reaction scheme:
A–B + C–D–E → A–D–B + C–E)

It is the latter, simpler, scheme which has been adopted. We consider rearrangements "intramolecular" as long as such a formalism properly accounts for product formation. Effects of catalysis are not normally considered to the end of establishing the $\tilde{R}$ matrix.

Another example of a change in reaction scheme, if account is taken of the reaction mechanism, is ORTON's rearrangement of halogenoamines:

$$C_6H_5 \cdot NClAc \xrightarrow{H^+} (o\text{- and } p\text{-})Cl \cdot C_6H_4 \cdot NHAc$$

Formally A–B + C–D → A–C + B–D, if considered as a true intramolecular rearrangement. According to the proposed mechanism:

$$C_6H_5 \cdot NClAc + HBr \leftrightarrows C_6H_5 \cdot NHAc + ClBr$$
$$C_6H_5 \cdot NHAc + ClBr \rightleftarrows$$
$$(o,p)BrC_6H_4 \cdot NHAc + HCl$$

the overall scheme is A–B + C–D + E–F → A–C + B–E + D–F. A similar reasoning holds for rearrangements of diazoamino-compounds, of nitrosamines (FISCHER–HEPP), *etc.*

In order to keep the subject matter within certain limits, such cases as non-isomeric rearrangements, common in the chemistry of allylic compounds, are considered as displacements accompanied by an anionotropic rearrangement. Thus, reactions as

$$CH_2{=}CH\text{–}CHMeCl \xrightarrow{NMe_3}$$
$$Me_3\overset{+}{N}CH_2CH{=}CHMeCl^-$$

(Reaction scheme:
A–B + C–D + E: → A–E + B–C + D:)

are not normally included in the Tables.

Not included in the paper either are results concerning molecular rearrangements which are not known in sufficient detail, *i.e.* most molecular rearrangements in heterocyclic compounds[9].

3. Results

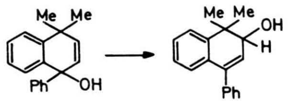
The classification of more than hundred of the most outstanding organic rearrangements according to their reaction electron-flow scheme and based on several reference works[10–13], is summarized in Tables I–III. It is clearly evident that $\tilde{R}1$ and $\tilde{R}2$ (Tables I and II) account for the majority of reactions investigated; this result is in accordance with findings for a more representative sample of about 1900 organic reactions[14]. Both $\tilde{R}$-matrices describe a great variety of rearrangements, ranging from nucleophilic and electrophilic rearrangements in saturated and unsaturated systems, to aromatic electrophilic, nucleophilic and intramolecular rearrangements and "no-mechanism" reactions.

A basis for discussion of isomerizations of linear unsaturated systems has recently been provided by ARENS[15]. From Figs. 4–7 in ref.[15] it is immediately obvious that intramolecular isomerizations (rearrangements) in linear C3 and C4 patterns are of the 1, 3 type and thus conform to $\tilde{R}1$. Similary, α, ε or 1, 5 isomerization is described by $\tilde{R}2$. In more extended systems higher order isomerization may occur which falls beyond the basis-set of $\tilde{R}$-matrices[14].

Most mono- and polydentate aromatic rearrangements of groups from the side-chain to the nucleus also conform to $\tilde{R}1$, such as the entries 17–24 of Table I. Typical examples of $\tilde{R}1$ type electron-flow schemes are the ring closure of cyclohexenyl-ethyl derivatives:

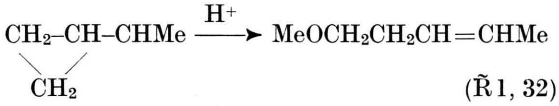
($\tilde{R}1$, 30)

and such reactions as



($\tilde{R}1$, 28)

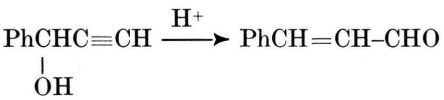
and



$$\underset{\diagdown\ CH_2\ \diagup}{CH_2\text{–}CH}\text{–}CHMe \xrightarrow{H^+} MeOCH_2CH_2CH{=}CHMe$$

($\tilde{R}1$, 32)

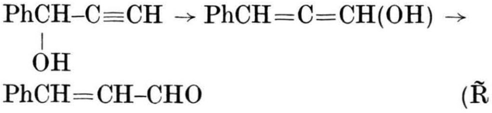
Instead, reactions in which the replacement occurs in a derivative ($\tilde{R}9$, 1) follow a different route. On the other hand, the apparently different electron flow in the acetylene-allene rearrangement according to MEYER–SCHUSTER ($\tilde{R}10$, 1):



$$\underset{\underset{OH}{|}}{PhCH}C{\equiv}CH \xrightarrow{H^+} PhCH{=}CH\text{–}CHO$$

($\tilde{R}10$, 1)

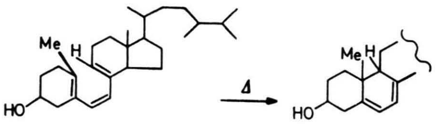
may be reconducted to 2*$\tilde{R}$1, namely



$$\underset{\mathrm{OH}}{\mathrm{PhCH}}\text{–C}\equiv\text{CH} \rightarrow \text{PhCH=C=CH(OH)} \rightarrow \text{PhCH=CH–CHO} \qquad (\tilde{R}1, 50)$$

Similary, the Rupe rearrangement ($\tilde{R}$1, 51) is essentially a 3*$\tilde{R}$1 process.

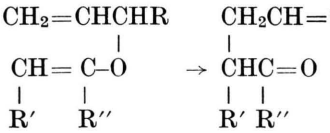
The Wagner–Meerwein and pinacolic rearrangements in acyclic and cyclic systems[16] which are in essence 1, 2 shifts of a group (alkyl, aryl or hydrogen), together with a pair of bonding electrons, may generally be classified according to $\tilde{R}$1 (entries 1, 3) or $\tilde{R}$2 (entries 1–7). Also anionotropic processes (tautomeric changes), and the earlier mentioned isomeric rearrangements in the chemistry of allylic compounds[17], $>$C=C–C–X, which may involve migration of a nucleophilic or anionic fragment from one potentially electrophilic center to another, mainly conform to these schemes ($\tilde{R}$1, 13, 28, 29, 50, 51; $\tilde{R}$2, 18, 19; $\tilde{R}$9, 1, 2). Typical $\tilde{R}$2-type reactions are the thermal conversion of precalciferol to (iso)pyrocalciferol:



($\tilde{R}$2, 13)

precalciferol (iso)pyrocalciferol

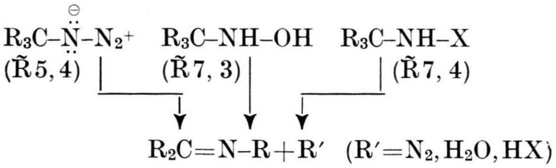
as well as



$$\begin{matrix}\text{CH}_2\text{=CHCHR} \\ | \\ \text{CH= C–O} \\ | \quad | \\ \text{R}' \quad \text{R}''\end{matrix} \rightarrow \begin{matrix}\text{CH}_2\text{CH=CHR} \\ | \\ \text{CHC=O} \\ | \quad | \\ \text{R}' \text{R}''\end{matrix} \qquad (\tilde{R}2, 19)$$

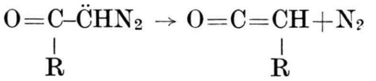
Also, the "no-mechanism" molecular reaction processes in which two or more bonds are broken and formed simultaneously, *e.g.* Claisen and Cope rearrangements, Diels–Alder reaction *etc.* are characterized by a very small variety of $\tilde{R}$-matrices, mainly $\tilde{R}$1 and $\tilde{R}$2.

Of the rearrangement reactions, without doubt the nucleophilic 1, 2 shift, in which a group migrates from one atom to an adjacent electron-deficient atom, has received most attention[18]. Typical examples of such, mainly classical carbon-to-nitrogen rearrangements are $\tilde{R}$5, $\tilde{R}$6, $\tilde{R}$7, $\tilde{R}$10, $\tilde{R}$13 and $\tilde{R}$15. The entries in the tables concern generally only the fundamental rearrangement steps in these processes, rather than the overall reactions. *E.g.* in the C to N rearrangements in azides, hydroxylamines and halo-amines we have considered:



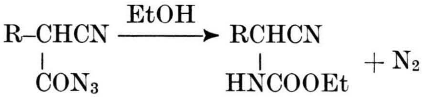
$$\text{R}_3\text{C–}\overset{\ominus}{\ddot{\text{N}}}\text{–N}_2^+ \ (\tilde{R}5, 4) \qquad \text{R}_3\text{C–NH–OH} \ (\tilde{R}7, 3) \qquad \text{R}_3\text{C–NH–X} \ (\tilde{R}7, 4) \quad \longrightarrow \quad \text{R}_2\text{C=N–R+R}' \quad (\text{R}'=\text{N}_2, \text{H}_2\text{O}, \text{HX})$$

Similarly, the fundamental step in the Wolff rearrangement, the conversion of an *α*-diazoketone into a ketene and nitrogen, has been taken as



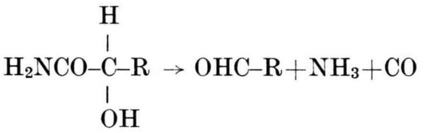
$$\text{O=}\underset{\text{R}}{\text{C}}\text{–CHN}_2 \rightarrow \text{O=C=}\underset{\text{R}}{\text{C}}\text{H+N}_2 \qquad (\tilde{R}5, 1)$$

The reaction matrix $\tilde{R}$15 is to be considered as an extension of $\tilde{R}$5, to which it stands in about the same relation as $\tilde{R}$1 to $\tilde{R}$2. In fact, the Schmidt reaction is related to the Curtius, Lossen and Hofmann rearrangements, whereas the Darapsky degradation is an extension of the Curtius reaction:



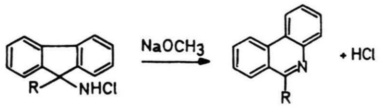
$$\underset{\text{CON}_3}{\text{R–CHCN}} \xrightarrow{\text{EtOH}} \underset{\text{HNCOOEt}}{\text{RCHCN}} + \text{N}_2 \qquad (\tilde{R}15, 2)$$

$\tilde{R}$13 is the reverse of $\tilde{R}$15 and the only example so far identified is the Weerman degradation:



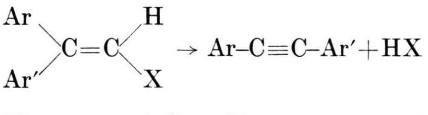
$$\text{H}_2\text{NCO–}\underset{\text{OH}}{\overset{\text{H}}{\text{C}}}\text{–R} \rightarrow \text{OHC–R+NH}_3\text{+CO} \qquad (\tilde{R}13, 1)$$

Most nucleophilic rearrangements collected under the heading $\tilde{R}$7 refer to 1, 2 shifts in carboxyl derivatives, but also comprise the rearrangement of haloamines, *e.g.*



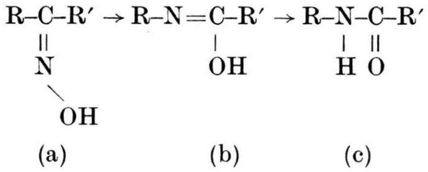
($\tilde{R}$7, 4)

and reactions such as those leading from 1,1-diaryl-2-halogen ethylenes with bases to form diarylacetylenes:



$$\begin{matrix}\text{Ar} \\ \text{Ar}'\end{matrix}\!\!>\text{C=C}\!\!<\!\!\begin{matrix}\text{H} \\ \text{X}\end{matrix} \rightarrow \text{Ar–C}\equiv\text{C–Ar}'\text{+HX} \qquad (\tilde{R}7, 5)$$

The classical C to N rearrangement of oximes, the Beckmann reaction[19]



$$\underset{\substack{\| \\ N \\ \setminus \\ OH}}{R-C-R'} \rightarrow \underset{\substack{| \\ OH}}{R-N=C-R'} \rightarrow \underset{\substack{|\;\;\| \\ H\;\;O}}{R-N-C-R'}$$

($\tilde{R}6$, 1)
($\tilde{R}1$, 49)

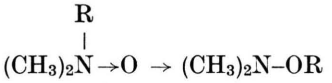
(a) (b) (c)

is characterized by an overall reaction (a) → (c) of the $\tilde{R}6$ type, although the single steps in the process each conform to $\tilde{R}1$.

Typical reactions of the $\tilde{R}10$ type are steps following up the carbon-to-nitrogen rearrangements, *e.g.*

$$RNCO + H_2O \rightarrow RNH_2 + CO_2 \qquad (\tilde{R}10,\ 3\text{–}5)$$

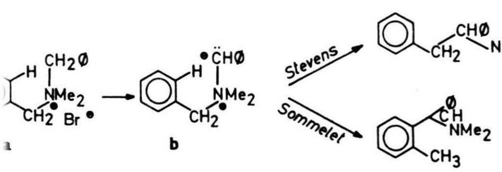
Least studied and less well understood are the electrophilic 1, 2 shifts in which the migration is to an adjacent atom bearing an active unshared electron pair and negative charge. Electrophilic rearrangements include oxygen-to-carbon migrations (Wittig rearrangement, $\tilde{R}1$, 6), nitrogen-to-carbon migrations (Stevens ($\tilde{R}12$, 1) and Sommelet rearrangements ($\tilde{R}8$, 1)), carbon-to-carbon migrations (Grovenstein–Zimmermann ($\tilde{R}12$, 2), Truce–Smiles rearrangements ($\tilde{R}1$, 7) and the skeletal rearrangement in the Bamford–Stevens reaction ($\tilde{R}5$, 5)), and a nitrogen-to-oxygen migration (Meisenheimer rearrangement ($\tilde{R}12$, 3)). An example of the latter is the base-catalyzed rearrangement of tertiary amine oxides to O,N,N-trisubstituted hydroxylamines:



$$(CH_3)_2\overset{\overset{\displaystyle R}{|}}{N}\rightarrow O \rightarrow (CH_3)_2N{-}OR$$

($\tilde{R}12$, 3)

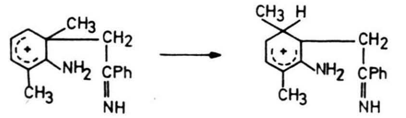
A good case of Stevens' and Sommelet's electrophilic nitrogen-to-carbon migrations is that of benzyltrialkylammonium compounds:



($\tilde{R}12$, 1)
($\tilde{R}8$, 1)

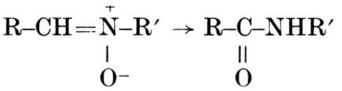
The real rearrangement is considered from (b) onwards as the reaction (a) → (b) may be described as an elimination reaction.

Most other reaction schemes of Table III refer to isolated rearrangements between systems at a great chemical distance (high electron flow). This is not the case of the migration of alkyl-groups in the Fischer indole synthesis:



($\tilde{R}11$, 1)

Reaction type $\tilde{R}14$ is illustrated by the formation of amides from nitrones, close relatives of oximes:

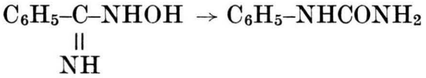


$$R{-}CH{=}\underset{\substack{| \\ O^-}}{\overset{+}{N}}{-}R' \rightarrow \underset{\substack{\| \\ O}}{R{-}C}{-}NHR'$$

($\tilde{R}14$, 1)

The carbon skeleton is not rearranged however, and the reaction appears to be a case of oxygen migration, unrelated to the Beckmann rearrangement.

Reaction type $\tilde{R}16$ has been attributed to the Tiemann rearrangement of amidoximes, *e.g.*

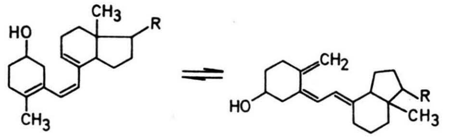


$$C_6H_5{-}\underset{\substack{\| \\ NH}}{C}{-}NHOH \rightarrow C_6H_5{-}NHCONH_2$$

($\tilde{R}16$, 1)

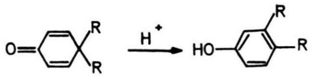
This reaction is actually complex[20] and $\tilde{R}16$ may be considered to be a linear combination of other electron flow schemes ($\tilde{R}1 + \tilde{R}6 + \tilde{R}10$).

An example of a rearrangement ($\tilde{R}17$) which appears to demand an eight-centered transition state in the reversible, thermal isomerization of previtamin D_2 to vitamin D_2, is:



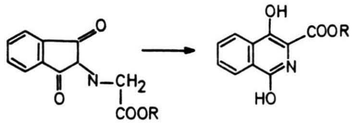
($\tilde{R}17$, 1)

Reaction scheme $\tilde{R}18$ describes two closely connected rearrangements, one of which, the dienone-phenol rearrangement, may be pictured as follows:



($\tilde{R}18$, 2)

As the only example of $\tilde{R}19$ we present the Gabriel–Colman rearrangement of phthalimidoacetic ester to isoquinoline:



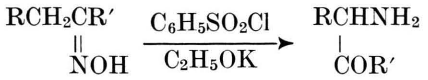
($\tilde{R}19$, 1)

The Wallach degradation, related to the Favorskii rearrangement, involves the base-catalyzed formation of 1-hydroxycyclopentano-carboxylic acids from *α,α'*-dibromocyclohexanones:

(cfr. $\tilde{R}20$, 1)

The rearrangement of the α,α'-dihydroxycyclohexanone intermediate follows the $\tilde{R}20$ scheme.

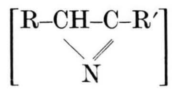
Finally, $\tilde{R}4$ has been observed in the formation of α-aminoketones from ketoximes (NEBER rearrangement):



$$\underset{\underset{\mathrm{NOH}}{\|}}{\mathrm{RCH_2CR'}} \xrightarrow[\mathrm{C_2H_5OK}]{\mathrm{C_6H_5SO_2Cl}} \underset{\underset{\mathrm{COR'}}{|}}{\mathrm{RCHNH_2}}$$

($\tilde{R}4$, 1)

and is related to the BECKMANN rearrangement ($\tilde{R}6$). If we admit the intermediate formation of azirines



the fundamental steps in the process may be visualized as $\tilde{R}1$ and $\tilde{R}10$.

4. Discussion

Examination of a representative subset of organic rearrangement reactions indicates that some twenty structural schemes (*i.e.* classes of $\tilde{R}$-matrices and not specific $\tilde{R}$-matrices) are sufficient for their description. Obviously, more significant data collections need to be examined before a complete set of reaction schemes can be formulated which is characteristic of the whole set of organic reaction types described in the literature. Similar information might prove to be valuable in computer-assisted synthesis planning as well as for the systematisation and codification of organic reactions.

With regard to the details of the set of $\tilde{R}$-matrices derived here, we notice that several of the observed reaction schemes, precisely $\tilde{R}4$, $\tilde{R}6$, $\tilde{R}13$, $\tilde{R}14$, $\tilde{R}16$, $\tilde{R}18$ and $\tilde{R}20$, were not detected in the sample of 1900 organic reactions mentioned above[14]. As evident from Table III, these $\tilde{R}$-matrices account for isolated reactions only. Actually, $\tilde{R}4$, $\tilde{R}6$, $\tilde{R}13$ and $\tilde{R}16$ may be considered as linear combination of other schemes.

As to the chemical constraints imposed by UGI *et al.*[6, 21] upon $\tilde{R}$-matrices, we notice that only 7 out of the 20 observed schemes comply with these restrictions, namely $\tilde{R}1$, $\tilde{R}2$, $\tilde{R}3$, $\tilde{R}8$, $\tilde{R}9$, $\tilde{R}11$ and $\tilde{R}12$; in terms of the fraction of reactions examined it appears that the constraints properly account for over 75% of the rearrangement reactions dealt with.

As to application in synthesis planning, the present analysis thus suggests the usefulness of a very restricted set of general $\tilde{R}$-matrices, covering a high percentage of the reactions investigated: roughly 80% of the organic rearrangements considered here appear to be described by 5 electron-flow schemes, namely $\tilde{R}1$, $\tilde{R}2$, $\tilde{R}5$, $\tilde{R}7$ and $\tilde{R}10$.

This implies greater control on the tree proliferation in precursor generation. Definition of an optimum set of $\tilde{R}$-matrices for this purpose must await other analyses on different and more extensive samples of organic reactions. Nevertheless, development of highly selective tree-pruning procedures for the evaluation of the nodes of the synthesis-tree is still of primary importance for the practical application of UGI's mathematical approach to synthesis planning.

5. Conclusions

In spite of their numerous kinds and complexities, the rearrangements of organic chemistry can be broken down into a relatively small set of electron-flow schemes or general reaction-matrix types, especially if we disregard the variety of $\tilde{R}$-matrices with small incidence. The analysis roughly corresponds to the nature of other samples of organic reactions. In particular, the preponderance of two main reaction types is in common to other random reaction files. The analysis differs obviously from others based on mechanistic concepts.

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