

seminars, within the same organizations.

Following end-user training, within an organization, many information specialists are reporting that they are actually busier than before and that the searches brought in are more challenging and better thought out by the scientist. The comments we receive from scientists are those of enthusiasm, appreciation, and awe of their newly learned power. Without question, these scientists should not be denied the training needed to access online scientific information.

As information grows in volume, it becomes more difficult to assimilate; but as it grows in volume, technology has made it easier to store, manipulate, and disseminate. The technology

that exists and the knowledge that online searching provides must be extended to all people that need it...the end users.

REFERENCES AND NOTES

- (1) Haines, J. S. "Experiences in Training End-User Searchers". *Online (Weston, Conn.)* 1982, 6, 14-23.
- (2) Meadow, C. T. "Online Searching and Computer Programming: Some Behavioral Similarities (or...Why End Users Will Eventually Take Over The Terminal)". *Online (Weston, Conn.)* 1979, 3, 49-52.
- (3) Richardson, R. J. "End-User Online Searching in a High Technology Engineering Environment". *Online (Weston, Conn.)* 1981, 5, 44-57.
- (4) Walton, R. W.; Dedest, P. L. "Experiences at Exxon in Training End-Users to Search Technical Databases Online". *Online (Weston, Conn.)* 1982, 6, 14-23.

TOSCA: A Topological Synthesis Design by Computer Application[†]

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TOSCA is a deductive method for the design of syntheses both in the forward and in the backward retrosynthetic direction. The use of strategic selection criteria makes it possible to use the system in particular in heterocyclic chemistry. It is shown by means of examples how empirical selection criteria lead to an intelligent reduction in the number of proposals. Structural features identified in precursors and the target of the synthesis form the basis for a further, subjective selection.

INTRODUCTION

Chemistry is an essentially experimentally and, hence, phenomenologically oriented science. Not surprisingly, the first synthesis design methods involving the use of computers were likewise empirically oriented, since they simulated the thought processes of the chemist by directly applying literature knowledge to an actual problem of synthesis.¹

This reasoning by analogy is effected in empirical synthesis design methods with the aid of a library of transformation instructions that has been derived from chemical reactions. The amount of work that is necessary to cover specific areas of chemistry in this way naturally increases with their complexity. The variety of heterocyclic chemistry makes it very time consuming to put together a suitable library of transforms. For this reason, we were interested in examining to what extent a mechanistic² or logic-oriented method³ might be suitable to cover the industrially important heterocyclic area.

The starting point for the development of such a method was an algebraic model of constitutional chemistry⁴ where synthesis proposals are generated by combinatorial changes to the bonds and bond orders between the atoms of given molecules. The number of transforms, i.e., transformation instructions, with this logic-oriented synthesis design method is much lower than that with the empirical method, since the electrons are manipulated purely combinatorially, that is, without consideration of the structure of the molecule and independently of the nature of the atoms.

However, a purely combinatorial procedure that only takes account of electron pairings produces not only proposals that can be interpreted in a chemically meaningful way but also so much more that is just garbage.

It is therefore necessary to resort to the computer-based application of selection criteria. For this purpose, we have differentiated the atoms according to potential donor or acceptor reactivities.

This differentiation makes it possible to select charge-controlled reactions. This strategic option is also associated with division into reactions which involve umpolung and those which do not.⁵ This concept, which is important in particular in the field of heterocyclic chemistry, is also important in extended areas of aliphatic chemistry.

In this way, the idea of combining a nonempirical method with selection criteria of universal validity is realized in TOSCA. Additional empirical selection criteria and interactive selection options then lead to a further reduction in the number of synthesis proposals.

IDEAS BEHIND TOSCA

Simulation of Reactions. The number of computer-generated precursors in a deductive synthesis design method is critically affected by (1) the decision about which of all the bonds present in the target of the synthesis are breakable, i.e., reactive, (2) the number of combinations of bonds to be broken in any one step that can be made from the set of all breakable bonds, and (3) the number of ways of recombining the reactive centers thus formed.

About 75% of all known chemical reactions involve the breaking and simultaneous forming of two or three bonds as depicted schematically in Figure 1.⁶

Such a method did not appear sufficient to be of wide applicability. For this reason, TOSCA incorporates an algorithm that permits up to 11 bond cleavages and 11 bond formations per reaction step. These numbers include the breaking and forming of multiple bonds. As in the majority of cases only two or three bonds are reoriented in a reaction, this method increasingly simulates reaction sequences in one step from four participating bonds onward.

Fundamental molecular changes are frequently difficult to keep track of. For this reason, TOSCA calculates the chemical distance between the individual precursors, which can then be arranged to form manageable reaction sequences. Identical precursors are automatically rejected in favor of the proposal involving the smallest shift of bonding electrons.⁷

[†] Dedicated to Professor Rolf Sammet on the occasion of his 65th birthday.

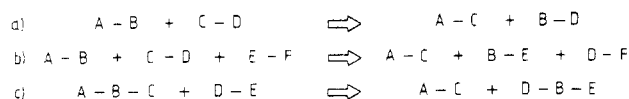


Figure 1. Schematic reactions involving the reorientation of two or three bonds.

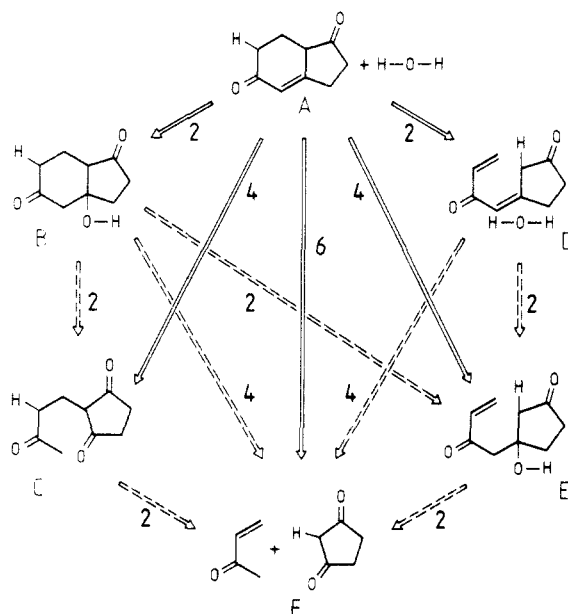


Figure 2. Arrangement of precursors into reaction sequences.

<u>CONSONANT REACTIONS:</u>	CHARGE-CONTROLLED REACTIONS	
	IONIC REACTIONS	
	NUCLEOPHILIC	} SUBSTITUTION
	ELECTROPHILIC	
	(POLAR CONDITIONS, ACID AND BASE CATALYSIS)	
<u>DISONANT REACTIONS:</u>	OXIDATION	} PROCESSES
	REDUCTION	
	UMPOUNG REACTIONS	

Figure 3. Definition of consonant and dissonant reactions.

This is illustrated by the comparatively simple example of a Robinson ring closure sketched in Figure 2. The breaking of successively two, four, and six bonds in starting compound A leads to precursors B-F. The corresponding arrangement, however, shows that B-E should be regarded as intermediates on the pathway to F.

In the present model, chemical reactions are understood as valence isomerization of a specified set of atoms. As this requires all the atoms that are involved in the reaction to be present, it is necessary to include beside the target molecule also the secondary components that are set free in the actual reaction, for example, H_2O in Figure 2.

In TOSCA this inclusion is effected partly or wholly automatically. To avoid double solutions, care is taken to ensure that all the chosen secondary components are involved in the reaction and that a starting secondary component is not reformed in the course of the reaction.

Strategies. The development of a strategy of universal validity is based on the fact that chemistry falls essentially into two parts.

One part covers consonant reactions and the other dissonant reactions,⁸ as is shown in Figure 3. Consonant reactions are charge-controlled reactions whose chemical driving force derives from the balancing out of different charges of normal

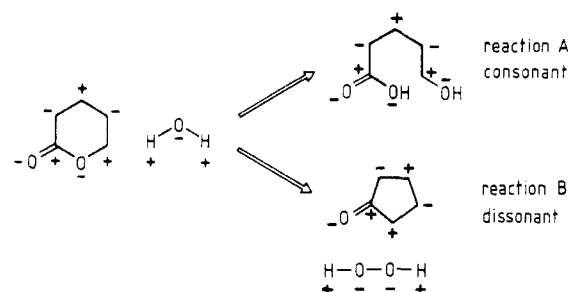


Figure 4. Example of a consonant reaction and a dissonant reaction.

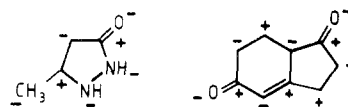


Figure 5. Examples of structures having dissonant bonds.

polarization. Dissonant reactions, on the other hand, also contain umpolung, oxidation, and reduction processes.

By consonant strategy is meant giving preference to consonant reactions. They generally take place under acid or base catalysis and frequently under readily realized reaction conditions. As charge-controlled reactions are equilibrium reactions, the principle of microscopic reversibility is applied. These reactions are therefore of equal suitability for a backward and a forward strategy and they go especially well with the deductive concept of generating reactions, which regards a reaction, irrespective of its direction, as an isomerization of the target of the synthesis. Consonant reactions take care of appreciable areas of heterocyclic, aliphatic, and aromatic chemistry.

The consonant strategy is incorporated in TOSCA in the simulation of reactions in the form of a recombination algorithm. It necessitates an analysis of the molecules containing heteroatoms in terms of their charge polarization and charge induction. As a result of this analysis, the atoms of a molecule, starting with the heteroatoms, are characterized with plus or minus labels according to their acceptor or donor properties, i.e., according to their electrophilic or nucleophilic character. Consonant reactions are then simulated by allowing only recombinations between centers of opposite signs (plus-minus) (Figure 4, reaction A). Dissonant reactions, on the other hand, additionally contain plus-plus or minus-minus recombinations (Figure 4, reaction B).

Target molecules that only consist of consonant bonds, i.e., in which no two adjacent centers have the same sign, are preferably dealt with by means of consonant reactions. Yet the consonant strategy is also suitable for targets that, from the analysis, contain not just plus-minus combinations.

By choosing the heteroatoms to be the starting point of the analysis, minus-minus combinations coincide with heteroatom/heteroatom bonds, and in addition, the plus-plus and minus-minus combinations are located in the carbon skeleton as far away as possible from the heteroatoms, so that suitable consonant reactions can be simulated.

If the consonant strategy is used, the dissonant bonds thus located are declared by the program to be unbreakable bonds. Strategically, this last step means that an attempt is made to shift the formation of a dissonant bond into a precursor and to use, if possible, a fitting educt that already contains this bond, for example, hydrazine or cyclopentandione for the synthesis of the compounds in Figure 5.

Another argument in support of the use of the consonant strategy is that these simulations can also cope with sequences of dissonant reaction steps. The division into consonant and dissonant reactions has consequences for the secondary components: (1) Consonant reactions can be described with the

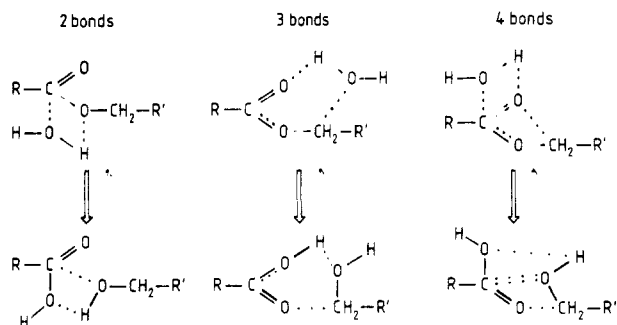


Figure 6. Isomorphous solutions differing in chemical distance.

aid of a limited number of secondary components that do not act as oxidizing or reducing agents. These are compounds such as H_2O , ROH , NH_3 , H_2S , HX , and CO_2 . (2) Besides the above-mentioned additives, dissonant reactions may also contain secondary components that cause oxidation or reduction processes.

For the simulation of simple oxidation or reduction processes, H_2 or O_2 are used as additives. For simulation of umpolung chemistry, use is made in particular of HX with reversed donor and acceptor properties.

Selection Criteria. For a variety of reasons, the simulated reaction can throw up chemically identical precursors. To keep the formation of these isomorphous proposals to a minimum in advance, certain atoms, such as, for example, hydrogen or halogen, and groupings of atoms, for example, methoxy groups, are equated in the simulation if they are present more than once. A reactive center is not allowed to recombine with a center from which it was separated or with an equivalent.

Any isomorphous solutions that remain are due to the fact that this method is not applicable to groupings that can freely enter either two single or one double bond or that different chemical distances are responsible for their appearance, as Figure 6 shows. These isomorphous solutions are eliminated by an identity comparison by analyzing the generated precursors and the individual parts of which they consist.

As ring openings, ring closures, and the growth or degradation of the carbon skeleton are some of the most important criteria of a reaction, the following features which have a bearing on the sorting of the synthesis proposals and the automatic construction of formula diagrams and are important as options in an interactive selection, are registered: (1) size of the carbon skeleton; (2) number of rings; (3) number of parts; (4) size of parts (number of atoms); (5) number of bonds in terminal chains; (6) number of bonds in chains that link rings in a molecule; (7) number of nonaromatic ring bonds; (8) number of aromatic ring bonds; (9) number of double bonds; (10) number of triple bonds.

Synthesis proposals that agree in the ten features are combined into groups. As this agreement is a necessary condition for two proposals to be isomorphous, the exact comparison of structures for the purpose of eliminating isomorphous proposals must only be carried out within the individual groups.

The exact comparison of structures is carried out by means of a specially developed search procedure that is based on a set-reduction algorithm.⁹ Unlike the atom-by-atom search, this procedure is very fast in the case of a successful search and, moreover, uses almost the same parameters as already required for simulating the reaction: (1) the type of atoms; (2) the number of ligands of an atom; (3) the order of the bond to the ligands; (4) the number of hydrogen atoms; (5) the number of bonds to heteroatoms (heterofunctionality). As already mentioned, the isomorph with the larger number of manipulated bonds is discarded.

The search algorithm also serves to eliminate tautomeric precursors. The unstable forms of tautomeric substructures

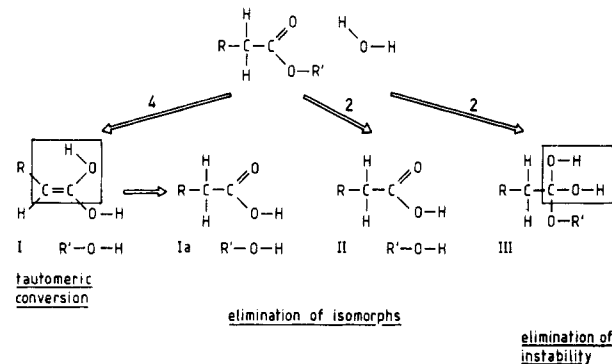


Figure 7. Empirical selection criteria.

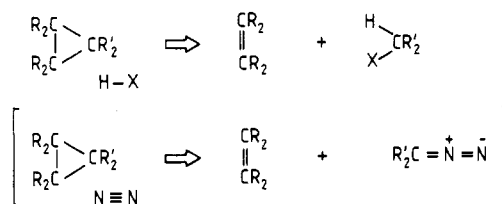


Figure 8. Fundamentally identical synthesis proposals based on different secondary components.

are on record in a data file. In several passes, these substructures, even if they overlap, are identified in the precursors and are converted into the more stable form. Should this in turn lead to isomorphous solutions, these are eliminated in the course of the identity search.

The synthesis proposals remaining after the elimination of isomorphs and tautomers are analyzed for structural elements that might be chemically unstable and, if any are found, are eliminated.

Figure 7 shows the elimination steps for the example of an ester synthesis. The number of bonds broken is shown above the arrows. Precursor I is transformed into Ia by tautomeric conversion and is then eliminated, since it is now identified as isomorphous to II. Precursor III is discarded because of the presence of an unstable structural element.

Further selections of universal validity are made by analyzing the ring structure for, for example, violations of the Bredt rule, the appearance of triple bonds, or the accumulation of multiple bonds in small rings.

Other instabilities such as hydrates, semiacetals, and mono- or diesters of orthoformic acid or orthocarboxylic acid are present in a substructure memory and are likewise ascertained by the set-reduction method⁹ and then removed.

Limitations. A synthesis design method that proceeds in the systematic manner described must be instilled with chemical life. Just how demanding this is on the knowledge and imagination of the chemist should become clear from the following.

To keep the number of synthesis proposals within manageable proportions, we imposed the restriction that the number of bonds on each reactive center in the simulated reactions should be a constant. This means not simulating reactions involving the appearance and/or disappearance of partial charges, free radicals, and free electron pairs. The alternative would be having to monitor through a second stage the merely reactive intermediates generated in the first stage. The consequence would be an exponential growth in the number of precursors. The secondary components, since they are to be applied at various places on a molecule, are universal in kind, as are consequently also the precursors produced therewith.

In our view, it was of minor importance whether, for example, the carbene required for addition across a double bond

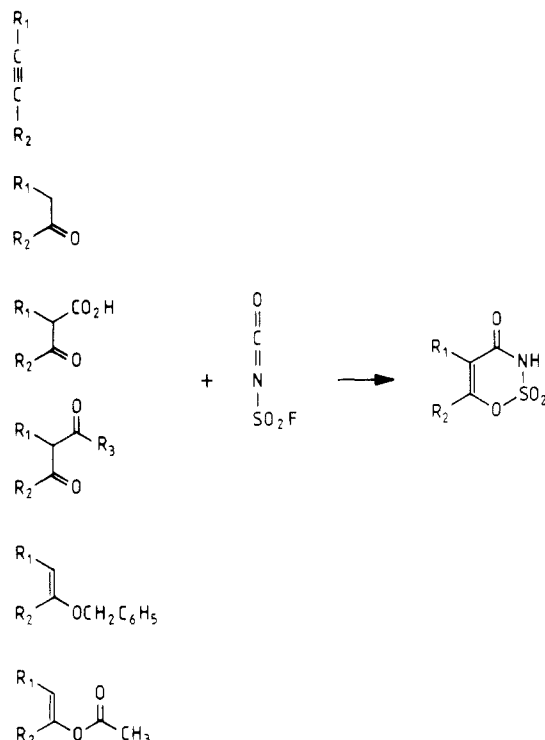


Figure 9. Reactions with fluorosulfonyl isocyanate leading to 3,4-dihydro-1,2,3-oxathiazin-4-one 2,2-dioxide derivatives.

is formed by α -elimination or the synthesis with diazomethane is additionally proposed (Figure 8).

The chemist is therefore free to supply a skillful interpretation of a synthesis proposal, such that he must find out, for example, which leaving group will be suitable for X or whether the proposed R-H should be realized as a CH acidic compound, an aromatic compound, or rather a Grignard compound and whether he would not be better off to use DMF in place of the formic acid proposed.

This is a clear illustration that the chief aspect in the development of TOSCA was the application of strategic structure-affecting reactions and that functionality changes play a minor part. TOSCA cannot specify reaction conditions or specific reagents. The relationship between the simulated reactions and the literature must also be established by the chemist. However, an automatic link to a reactions file is provided and has also been checked by means of the above-mentioned search procedure.

The changes in the electron pairings leading from the target molecule to the precursors are known. Through additional consideration of the symbols for the elements, the comparison with a suitably encoded reactions file then leads to the retrieval of known reactions.

EXAMPLES

The following example is intended to show that TOSCA can provide meaningful answers to retrosynthetically posed questions. The reaction of acetylenes, ketones, 3-keto acids, 1,3-dicarbonyl compounds, benzyl vinyl ethers,¹⁰ or enol acetates¹¹ with fluorosulfonyl isocyanate and subsequent treatment with base led to the heterocyclic compounds mentioned in Figure 9, which have been found to be potential sweeteners.

The search was for alternative methods of synthesizing the specific representative 3,4-dihydro-6-methyl-1,2,3-oxathiazin-4-one 2,2-dioxide (R_1 , H; R_2 , CH_3). The restrictions concerning the breakable bonds were imposed as follows: (1) From previously performed reactions, it appeared to be advisable to use the consonant strategy. (2) The selected sec-

principal component	secondary components H-O-H H-X O=C=O	synthesis proposals (selection from 701 proposals)
 3,4-dihydro-6-methyl-1,2,3-oxathiazin-4-one 2,2-dioxide	— — —	
	1 — —	
	— 1 —	
	— 2 —	
	1 1 —	
	— — 1	
	— 1 1	

Figure 10. Partly realized proposals¹² for further reactions leading to 3,4-dihydro-6-methyl-1,2,3-oxathiazin-4-one 2,2-dioxide.

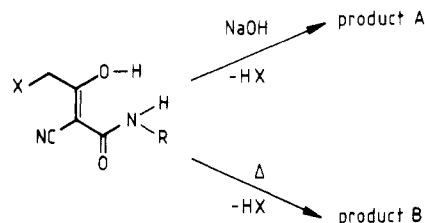


Figure 11. Products of unknown structure through elimination of HX from 4-halogeno-2-cyanoacetoacetamide derivatives.

ondary components were HX, which has one breakable bond, and H_2O and CO_2 , which each have two breakable bonds. (3) The combination of two additives in which, as, for example, in $H-O-H$ and $O=C=O$, a maximum of six breakable bonds occurs was not permitted. The number of breakable bonds in all additives was limited to three, e.g., in the case of $H-X$ and $H-O-H$. (4) The breakable bonds in the main component were selected in such a way that the simulation did not cover previously discovered reactions.

The selection, shown in Figure 10, of 701 precursors left over after tautomers, isomorphs, and instabilities had been eliminated shows that for each of the secondary components the proposals that are generated make sense and are of interest to the chemist.

Up to now we have only discussed retrosynthesis. Yet, according to the principle of systematic bond isomerization, TOSCA can also be used for solutions in a forward-directed approach. This will be illustrated by reference to the example depicted in Figure 11, in association with the meaningful application of empirical and subjective selection criteria.

	Subjective Selection Criteria			
Empirical Selection Criteria	none	2 parts at most 1 ring	2 parts 1 part = H X	2 parts at most 1 ring 1 part = H X
none	827	297	157	108
isomorphous	491	183	93	69
unstable	122	18	21	6
anti-Bredt	11	0	3	0
Summary	203	96	40	33
	open-chain structures			of which
	three - ring "			12
	four - ring "			6
	five - ring "			3
				12

Figure 12. Number of products proposed from 4-halogeno-2-cyanoacetoacetamide derivatives as a function of applied restrictions (after elimination of tautomers).

4-Halogeno-2-cyanoacetoacetamide derivatives eliminate hydrogen halide in the presence of a base or under heat, leading to different products whose structure was sought.¹³ It was possible to restrict the scope of the search as a result of the following deliberations: (1) As a strongly polar byproduct is formed in HX, the consonant strategy was used. (2) As a consequence, a dissonant bond in the educt was classified by the program as unbreakable. As, from the spectroscopic data, the nitrile group was still present in both the products, its bonds were likewise defined as unbreakable. (3) Since HX is eliminated, it follows that it was only necessary to look for proposals consisting of two parts of which one was HX. (4) Because of their molecular size, the products could contain no more than one newly formed ring.

The number of products proposed under these restrictions is listed in Figure 12. This number is cut appreciably by elimination on the grounds of structural isomorphism, substructure instability, and Bredt rule violation.

Of 33 structures that remain in the end, there are 21 that contain no five-membered ring. These are less probable.

Of the five-ring compounds depicted in Figure 13, structures 5 and 6 turned out to be the actual reaction products. The two structures have not yet been assigned to either product A or B.

Priority was given to the complete elimination of tautomerism. For this reason, some of the five-ring structures depicted may not be the thermodynamically most stable representatives.

CONCLUSIONS

It has been shown by means of examples that TOSCA can find solutions to problems in heterocyclic chemistry. The consonant strategy was found to be advisable for this field and

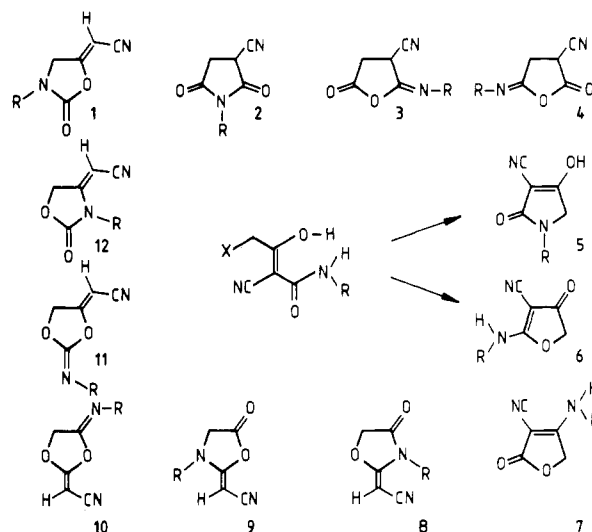


Figure 13. Five-ring structures proposed for reaction products A and B.

led to an appreciable reduction in the number of proposals.

In reality, reactions, in particular in heterocyclic chemistry, are predominantly of normal polarity. Where umpolung does take place, it generally occurs at most at one or two centers. Without the use of the consonant strategy, the simulation of reactions involving 11 bond cleavages and recombinations led not only to an overrepresentation of the dissonant type but also to the proposal of many absurd solutions.

Tests to data therefore appear to justify the approach of taking account of dissonant reactions by including one or at

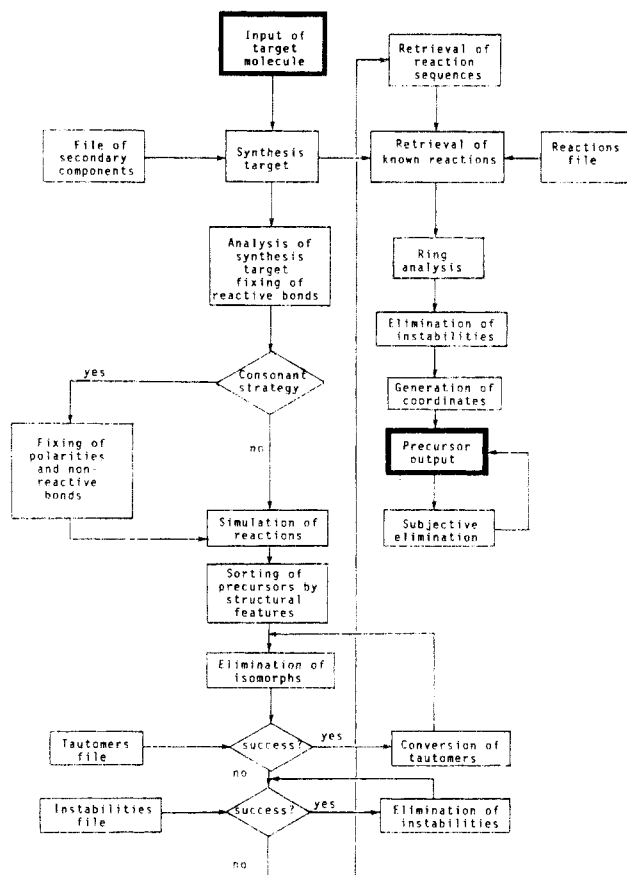


Figure 14. TOSCA flowchart.

most two plus-plus and/or minus-minus recombinations in addition to the plus-minus recombinations customary in consonant reactions.

Only this procedure, supported by the selection criteria discussed above, made it possible to handle bond isomerization involving up to 11 bonds within a manageable order of magnitude. This has been demonstrated not only for problems of synthesis but also for problems of retrosynthesis by using TOSCA, for example, to clarify structures and to play through procedural variants that are difficult if not impossible to deal with by empirical synthesis design.

TOSCA, furthermore, has been found to be particularly useful wherever no account needs to be taken of secondary components. This is chiefly the case with addition and rearrangement reactions. TOSCA can also be used in aliphatic and cycloaliphatic chemistry, but it is particularly useful for the simulation of polar reactions in heterocyclic chemistry.

DETAILS OF THE PROGRAM SYSTEM

This work was carried out within the period 1976–1980. The TOSCA program package is made up of 45 individual programs, which consist of about 20 000 Fortran and about 3000 assembler statements and occupy about 2000 pages each of which has a storage capacity of 2048 characters. The

programs were developed on a Siemens 4004/150 using the BS 2000 operating system and on a Univac 90/80-4 using the VS 9 operating system. Input is via a keyboard or graphic terminal, and the graphic output is via screen (Imlac, Tektronix, DEC GT44) or plotter (Calcomp). The program manipulates molecules under the following limitations: atoms per target or precursor, 75; number of bonds per target or precursor, 75; number of ligands per atom, 10; number of molecules per target or precursor, 9; atomic numbers, 1–57, 72–89; number of rings per molecule, 10; number of systems of rings per molecule, 5; number of atoms in a ring, 50; number of chains that link rings, 9; number of atoms per chain that link rings, 15. The flowchart of the program is depicted in Figure 14.

REFERENCES AND NOTES

- (1) Corey, E. J. "Computer-Assisted Analysis of Complex Synthetic Problems". *Q. Rev.* **1971**, *25*, 455. Wipke, W. T.; Braun, H.; Smith, G.; Choplin, F.; Sieber, W. "Computer-Assisted Organic Synthesis". *ACS Symp. Ser.* **1977**, No. 61. Bersohn, M.; Esack, A. "Computers and Organic Synthesis". *Chem. Rev.* **1976**, *76*, 269. Gelernter, H.; Bagwat, S. S.; Larsen, D. L.; Miller, G. A. "Knowledge-Base Enhancement via Training Sequence: The Education of SYNCHM2". *Anal. Chem. Symp. Ser.* **1983**, *15*, 35–59. Long, A. K.; Rubenstein, S. D.; Joncas, L. J. "A Computer Program for Organic Synthesis". *Chem. Eng. News* **1983**, May 9.
- (2) Hendrickson, J. B.; Braun-Keller, E.; Toczko, G. A. "A Logic for Synthesis Design". *Tetrahedron* **1981**, *37* (Suppl. 1), 359. Hendrickson, J. B. "Computer Implementation of Systematic Synthesis Design". Presented at the Annual Chemical Congress of the Royal Society of Chemistry, Exeter, April 18, 1984. Moreau, G. "MASSO, un Programme d'Aide à la Synthèse Organique Utilisant des Demi-Réactions". *Nouv. J. Chim.* **1978**, *2*, 187. Schmidt Burnier, J.; Jorgensen, W. L. "Computer-Assisted Mechanistic Evaluation of Organic Reactions. 8. General Treatment of Periselectivity". *J. Org. Chem.* **1984**, *49*, 3001. Weise, A.; Scharnow, H. G. "Ableitung organisch-chemischer Reaktionen mit dem Simulationsprogramm AHMOS". *Z. Chem.* **1975**, *15*, 333.
- (3) Blair, J.; Gasteiger, J.; Gillespie, C.; Gillespie, P. D.; Ugi, I. "Representation of the Constitutional and Stereochemical Features of Chemical Systems in the Computer Assisted Design of Synthesis". *Tetrahedron* **1974**, *30*, 1845. Gasteiger, J.; Jochum, C. "EROS—A Computer Program for Generating Sequences of Reactions". *Top. Curr. Chem.* **1978**, *74*, 93. Schubert, W.; Ugi, I. "Darstellung chemischer Strukturen fuer die Computer-gestuetzte deduktive Loesung chemischer Probleme". *Chimia* **1979**, *33*, 183.
- (4) Dugundji, J.; Ugi, I. "An Algebraic Model of Constitutional Chemistry as a Basis for Chemical Computer Programs". *Top. Curr. Chem.* **1973**, *39*, 19.
- (5) Seebach, D. "Methods of Reactivity Umpolung". *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
- (6) Bart, J. C. J.; Garagnani, E. "Organic Reaction Schemes and General Reaction-Matrix Types. IV. Organic Name Reactions". *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1977**, *32B*, 678.
- (7) Jochum, C.; Gasteiger, J.; Ugi, I. "The Principle of Minimum Chemical Distance (PMCD)". *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 495.
- (8) Evans, D. A. "Consonant and Dissonant Relationships. An Organizational Model for Organic Synthesis". UCLA Physical Organic Chemistry Seminar, May 6, 1971; *Acc. Chem. Res.* **1974**, *7*, 147. Serratos, P. F. "Synthesis and Biosynthesis of Dissonant Molecules: Reactivity Inversion". *Bull. Soc. Catalana Cienc. Fis., Quim. Mat.* **1977**, *1*, 75; *Chem. Abstr.* **1978**, *89*, 1963415.
- (9) Sussenguth, E. H. "A Graph-Theoretic Algorithm for Matching Chemical Structures". *J. Chem. Doc.* **1965**, *5*, 36.
- (10) Clauss, K.; Jensen, H. "Oxathiazinone Dioxides—A New Group of Sweetening Agents". *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 869.
- (11) Report DE-OS 2434547, HOECHST AG, January 29, 1976.
- (12) Report DE-OS 2447201, HOECHST AG, October 2, 1974. Kampe, K.-D. HOECHST AG, unpublished results.
- (13) Kampe, K.-D. HOECHST AG, unpublished results.