

IGOR AND RAIN - THE FIRST MATHEMATICALLY BASED MULTI-PURPOSE PROBLEM-SOLVING COMPUTER PROGRAMS FOR CHEMISTRY AND THEIR USE AS GENERATORS OF CONSTITUTIONAL FORMULAS

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Theoretical Chemistry ?

Mathematics mainly entered chemistry via physics and its theories. In general, mathematical theories of physics are quantitative in nature. These theories are useful for the interpretation and prediction of numerical experimental results. In physics and related sciences it is widely believed, that a "theory" is no real theory, if it is not suitable for predicting numerical observables. Quantum chemistry, the theoretical physics of molecules, and also numerous other physics-based quantitative mathematical theories and methods play an important role in chemistry.

The classical chemical problems, like synthesis design or the elucidation of reaction mechanisms, are qualitative and combinatorial in nature and they have generally many solutions. These solutions are molecular systems or chemical reactions, and they are found by *chemical reasoning*. Chemical reasoning proceeds to a large extent by analogy and combinatorial procedures; it is based on knowledge, experience as well as imagination and intuition.

Chemistry seems to have no theory of its own that deserves the name "theoretical chemistry". There is no uniform theory that may serve to directly solve classical chemical problems, a theory that covers all of chemistry, that is sufficiently rigorous and formal, and that is capable of predicting the conceivable existence of molecular systems with specified structural features or intermolecular relations.

Quantum chemistry helps to understand many facts and phenomena in chemistry, and - with the aid of computers - yields numbers that can be compared with numerical results of measurements involving well-defined chemical systems. Clearly, quantum chemistry is not able to directly solve classical chemical problems with a strong combinatorial aspect. Nevertheless, the terms *theoretical chemistry* and *quantum chemistry* are often used as synonyms. *Theoretical chemistry* ought to be a discipline that encompasses all conceptual, formal and logic based approaches to chemistry.

Traditional Mathematical Chemistry

Mathematical chemistry has a long history that began with the graph theoretical representation of molecules by Cayley¹ and Sylvester² as well as the group theoretical enumeration of isomers by Lunn and Senior³ and by Pólya⁴. However, only in the past 20 years mathematical chemistry has become an accredited discipline of science with its own conferences, journals and even chairs. Computers have enhanced the scope of mathematical chemistry⁵⁻⁷.

The objective of mathematical chemistry is the direct solution of chemical problems by formal methods. The qualitative concepts, models and theories of mathematical chemistry provide formal approaches to chemistry and its problems without the intermediacy of physics.

Traditionally, molecules and families of molecules, static objects of chemistry, are the considered objects. The qualitative use of mathematics is here, in essence, confined to visualization and representation of chemical objects by graph theory⁸ as well as their classification⁹ and enumeration^{4,9,10} by group theory.

The importance of a direct and detailed back and forth translation of chemistry, including the interconversions of molecular systems by chemical reactions, into qualitative formal representations has generally been underestimated. Thus, mathematical chemistry has not been understood and accepted by chemists as widely as it deserves, and it has not received sufficient input from chemists in terms of general insights and worthwhile problems. Much progress can be expected from an intensive and close collaboration of qualified mathematicians and chemists. Teams of closely cooperating representatives of both disciplines will be more effective and productive than mathematicians who have familiarized themselves with chemistry, or chemists who have acquired some mathematical background. Full proficiency without

dilettantism in any one of the disciplines is only achievable through meaningful collaboration.

The need for interdisciplinary collaboration is illustrated by the fact that in the field of isomer enumeration the record of mathematical achievements is superb, but the chemical part is not satisfactory, because until 1970¹¹ the various types of isomers were not clearly defined; some authors enumerated "stereoisomers", while in reality they were dealing with permutation isomers¹². When computers are involved, computer expertise is needed together with suitable computer hardware and software. The DENDRAL project⁵ would have presumably been more successful if present-day hardware and software technology had been available.

Although in the solution of genuine chemical problems the dynamic aspect of chemistry - chemical reactions and other changes that molecules may undergo - must definitely be accounted for, traditional mathematical chemistry does not provide any means for the explicit and detailed representation of the very events and processes by which distinct molecules are interconverted. Customarily, even in the treatment of dynamic changes, only the static structural features of the participating species are registered, and, as a rule, the processes by which the chemical changes occur, are not included in the common qualitative mathematical approaches to chemical problems.

The Static and Dynamic Aspects of Chemistry

The difference between a static and a dynamic viewpoint is illustrated by the historical example of Berry Pseudorotation (BPR)¹³ and Turnstile Rotation (TR)¹⁴. About 20 years ago, the reorganizations of phosphorane derivatives were very much *en vogue* among stereochemists and mathematically inclined chemists^{12,15}. These processes were represented and discussed in terms of the so-called Musher Modes¹⁶. The Musher Mode of a given type of isomerization consists of those distinct isomers that are directly interconvertible with the chosen reference isomer. A Musher Mode is mathematically represented by the union of those ligand permutations that lead from the reference isomer to the direct products of the considered process. In the corresponding reaction graphs the edges indicate the interconvertibility of the molecules that are represented by the connected nodes. This is the description of a dynamic process by static entities. When F. Ramirez, I. Ugi et al.¹⁴ inspected the individual permutations that belong to the Musher Mode of the BPR, they realised that each permutation represents a particular intramolecular motion, and that the permutations within a

BPR Musher Mode that lead from a given molecule to a specified isomer belong to two distinct Wigner subclasses¹⁷. Chemically one subclass belongs to the BPR and the other subclass represents a different type of intramolecular motion, the so-called TR.

When this observation was published¹⁴, one of the most passionate and prolonged controversies in the history of modern chemistry was touched off. It was mainly based on a misunderstanding. One party claimed that, in some cases, the TR mechanism must be considered besides the BPR¹⁴, while the other party insisted that only the BPR mode must be considered, and nothing else¹⁸. In this dispute the parties operated in their own distinct worlds of concepts. One party relied on a static description and classification of molecular reorganization where only the isomers count, while the other party invoked a dynamic picture of the processes where each permutation of the ligands is an individual isomerization, and permutations with the same cycle structure form mechanistic equivalence classes. The controversy seems to have subsided after a clarifying article¹⁹ appeared in 1988.

According to present knowledge, some phosphorane derivatives prefer intramolecular reorganization by BPR, others by TR, depending on the respective set of ligands¹⁹. Generally, it is of little practical consequence whether BPR or TR is the reorganisation mechanism. However, the TR/BPR case had a beneficial effect by having enhanced awareness of the differences between a static and a dynamic view of chemistry. It was an important stimulus in the formulation of the theory of Chemical Identity Groups (CIG theory)¹². It lead to a profound insight: when the dynamic aspect of a chemical problem is essential, the traditional static approach does not always suffice. Then a distinct approach with a suitable framework of new concepts is needed.

In the sequel, the importance of *permutational isomerism*¹¹ became increasingly apparent. Elementary geometry and point group symmetry were replaced by the more abstract concept of *chemical identity* as the conceptual basis for unifying static and dynamic stereochemistry. This encompassed a modified notion of chirality²⁰ and the indexing of ligands only²¹ instead of the previous use of skeletal indices alone or in combination with ligand indices. These concepts are prerequisite for the qualitative mathematical treatment of the dynamic aspect of stereochemistry by set-valued mappings of co-set spaces of the so-called chemical identity groups^{12,22-25}.

With their contributions to stereochemistry J. Dugundji, I. Ugi et al.^{12,26} introduced two new elements into mathematical chemistry, the dynamic view together with a corresponding mathematical representation of chemistry, and the

emphasis on a transparent translation of chemistry into mathematics and *vice versa*.

A system of computer programs for the solution of a wide variety of stereochemical problems on the basis of the CIG-theory is being developed. This system will be able to generate representations of families of stereoisomers and permutation isomers and the considered relations between these. The dynamic aspect of stereochemistry is adequately considered by the set-valued mappings that are part of the CIG-theory.

The Logical Structure of Constitutional Chemistry and its Mathematical Representation

Experience with the unified theoretical approach to stereochemistry stimulated the formulation of a mathematical representation for constitutional chemistry, too. The dynamic aspect of constitutional chemistry is taken into account by representing molecules and ensembles of molecules (EM) by so-called BE-matrices (**B**ond and **E**lectron matrices) with well-defined transformation properties, and a detailed description of the electron redistribution processes during chemical reactions by transformations of the BE-matrices. Until the advent of the theory of the BE- and R-matrices²⁶, briefly the DU-Model, (it is quoted in the literature^{27,28} as the Dugundji-Ugi-Model) the mathematical treatment of constitutional chemistry was limited to the description of the static constitutional features of molecules by graph theory⁸.

In 1973, J. Dugundji and I. Ugi published the theory of the BE- and R-matrices, an algebraic model of the logical structure of chemistry that covers both, the static and the dynamic aspects of constitutional chemistry. In contrast to the traditional qualitative mathematical approaches, the DU-model and the CIG-theory do not only deal with given molecules but also with their interconversions by chemical reactions. Thus the DU-model and the CIG-theory provide a very effective interface between mathematics and chemistry, and these theories contain mechanisms for the direct translation of chemical objects and phenomena into mathematics and *vice versa*. Accordingly, chemical problems can be translated into mathematical problems that can be solved by mathematical means and with computer assistance. The DU-model introduced some new elements into mathematical chemistry: to our best knowledge, it is the first global qualitative mathematical theory of chemistry as a unified entity. The DU-model explicitly represents the redistribution of valence electrons during chemical reactions by transformations of matrices that represent the static

chemical constitution of the reactants. Moreover, in contrast to most previous mathematical approaches to chemistry, the DU-model comprizes a detailed back and forth translation between chemistry and mathematics at all levels. In fact, within the framework of the DU-model and its applications the chemical and mathematical aspects are always equally emphasized. The DU-model may be seen as a mathematical foundation for formalized and systematic chemical reasoning.

The DU-model serves as the mathematical basis of the complementary computer programs IGOR (Interactive Generation of Organic Reactions)²⁹⁻³¹ and RAIN (Reactions And Intermediates Networks)³²⁻³⁶. Unlike the other hitherto implemented problem-solving computer programs in chemistry, IGOR and RAIN are not dedicated to the solution of any specific type of problem, e.g. the design of syntheses. On the contrary, together, they have a wide range of chemical applications and, due to their great versatility, they may be called *multi-purpose programs*.

The solution of chemical problems on the basis of the DU-model is achieved by solving the fundamental equation of this theory.

$$\mathbf{B} + \mathbf{R} = \mathbf{E}$$

Here \mathbf{B} and \mathbf{E} are BE-matrices that represent the chemical constitution of the educts $EM_{\mathbf{B}}$ at the beginning of the reaction and the products $EM_{\mathbf{E}}$ at the end of the reaction. Each row/column of \mathbf{B} and \mathbf{E} belongs to an atom of $EM_{\mathbf{B}}$ and $EM_{\mathbf{E}}$, respectively, and the integer entries of \mathbf{B} and \mathbf{E} indicate formal covalent bond orders and placements of the free valence electrons at the individual atoms. The transformation of \mathbf{B} into \mathbf{E} by addition of \mathbf{R} represents the electron redistribution during the reaction $EM_{\mathbf{B}} \Rightarrow EM_{\mathbf{E}}$.

The equation $\mathbf{B} + \mathbf{R} = \mathbf{E}$ can be solved by a given BE-matrix, say \mathbf{B} . Then these so-called B-solutions are the pairs (\mathbf{R}, \mathbf{E}) that satisfy the equation under specified boundary conditions. The above equation can also be solved by a given R-matrix \mathbf{R} ; the respective R-solutions are the pairs (\mathbf{B}, \mathbf{E}) .

The equation $\mathbf{B} + \mathbf{R} = \mathbf{E}$ generally has a very large number of solutions that can be found with the aid of computers. This is accomplished by so-called Reaction Generators of type B and R (RG B and RG R).

Transition table guided RGs, TRG B³⁴ and TRG R^{29,31}, are the engines of IGOR 2 and RAIN 2, the current versions of our computer programs for solving chemical problems. The transition tables in the TRGs ensure that only those solutions of $\mathbf{B} + \mathbf{R} = \mathbf{E}$ are generated which involve allowable valence schemes

of the considered chemical elements and their permitted transitions³². The DU-model does not only enable the generation of solutions of chemical problems but is also useful for selecting the most plausible results³⁷.

The computer programs IGOR and RAIN were primarily designed to solve a wide range of problems that involve chemical reactions. However, in particular operating modes, these programs can also be used as *structure generators* that elaborate collections of constitutional formulas according to specifications by the user.

In this article the generation of constitutional formulas by IGOR and RAIN is presented.

The Munich Project

The present authors are implementing the Munich Project^{32,38}, a master plan that is based on the philosophy of equal emphasis on chemistry, mathematics and computer science. It involves the formulation of a global qualitative mathematical model of chemistry as well as the development of computer programs for the solution of chemical problems on the basis of this model. Furthermore, the Munich Project includes the testing and use of the latter computer programs and the experimental realization of computer-generated results and solutions of chemical problems.

The DU-model was the first building block of the Munich Project, and it still is its cornerstone. In the meantime several modifications²⁸ and extensions³⁹ of the B DU-model have been formulated.

The concept of equally emphasizing chemistry and mathematics is illustrated by the algorithm and corresponding computer program CANON^{12,39} for unique indexing of atoms in molecules. Constitutional chemical formulas are multigraphs whose labelled nodes correspond to atoms and whose edges represent the covalent bonds; the free valence electrons are indicated by "loops". In CANON the labels of the nodes, the chemical element symbols, are taken into account simultaneously with the underlying graph.

In contrast, the Morgan algorithm of CAS⁴⁰ processes the graph first, and then, in a second step, it accounts for the distinct chemical elements to which the individual atoms belong. As a consequence, CANON is clearly more efficient in recognizing constitutional equivalencies and symmetries⁴¹.

Thus CANON is also suitable for ligand indexing in stereochemistry¹², instead of the CIP sequence rules⁴². The computer assisted use of the CIP rules, in particular in their original form, is rather cumbersome, because in their design

bond orders were considered instead of coordination numbers, and chemical considerations prevailed over mathematical and algorithmic considerations.

CANON is part of the software infrastructure of the Munich Project. It leads to unique representations of molecules and serves in the internal documentation moieties of all computer programs that belong to the Munich Project. In IGOR and RAIN redundancies are avoided through CANON. Furthermore, the efficiency of the RGs is increased by the exploitation of the atomic equivalence classes that are produced as a side product of the application of CANON. The atomic indices that are generated by CANON seem to be almost inherent and natural to chemistry.

The Historical Development of Computer-Assisted Generation of Chemical Formulas

Computer-assisted generation of chemical formulas according to given specifications is an important topic of mathematical chemistry and computer chemistry, because it has a great variety of applications in chemistry and it still poses many challenging problems.

There are two approaches to the computer-assisted generation of chemical formulas. The first is, in essence, based on a qualitative mathematical representation of chemistry. The second approach assembles chemical formulas with the aid of a file of standard substructures.

The literature on the computer-assisted generation of chemical formulas has been comprehensively reviewed in 1986 by Gray⁶.

The development of mathematically based computer programs for generating formulas of constitutional isomers was initiated by Lederberg⁴⁴ as part of the DENDRAL project⁵ for computer-assisted structure elucidation from spectroscopic data. Gribov⁴⁵ and Sasaki⁴⁶ recognized the advantages of procedures that could assemble chemical formulas from standard substructures which are present in a considered molecule according to spectroscopic data.

A structure generator must proceed in an exhaustive and irredundant manner, i.e. it must guarantee that all allowable structures are considered and that no duplicate structures are produced.

The first complete solution to the problem of exhaustive and irredundant structure generation was based on Lederberg's matrix graph formulation⁴⁴, and was implemented in the computer program CONGEN⁴⁷. GENOA⁴⁸, the most recent structure generating program of the DENDRAL project evolved from CONGEN. CHEMICS⁴⁹ is the most recent structure generating and structure

elucidating program that is based on a set of predefined multiatomic substructural fragments. CASE⁵⁰, STREC⁵¹ and SEAC⁵² are similar computer programs. Recently, two essentially graph theory based computer programs for generating constitutional formulas have been described, MOLGRAPH by Kerber et al.⁷, a program that is capable of handling large numbers of molecular graphs, as well as a program by Hendrickson and Parks⁵³ for generating carbon skeletons.

Generation of Constitutional Formulas by IGOR

The computer program IGOR^{23,29-32} has been implemented for the generation of chemical reactions. IGOR is based on a mathematical model of the logical structure of constitutional chemistry^{23,26} and does not rely on a file of stored empirical chemical data. It generates chemical reactions from electron redistribution patterns that are represented by so-called irreducible R-matrices \mathbf{R}^i that result from R-matrices \mathbf{R} by removal of all rows and columns without non-zero entries. The rows/columns of irreducible R-matrices belong to the reactive centres which directly participate in the bond breaking/making processes. Thus an irreducible R-matrix refers to the core of a reaction, i.e. the set of reactive centres in the EM that participate in the given reaction²³. It contains no zero rows/columns. IGOR produces chemical reactions from an input irreducible R-matrix \mathbf{R}^i by generating those pairs (\mathbf{B}, \mathbf{E}) of BE-matrices that are solutions of the equation $\mathbf{B} + \mathbf{R} = \mathbf{E}$ under the valid boundary conditions^{30,31}.

When the input matrix \mathbf{R} is the zero matrix ($\mathbf{R}=0$), we have $\mathbf{B} = \mathbf{E}$. Then IGOR generates all constitutional formulas that comply with the specifications defined by the user.

IGOR 2³¹, the most recent version of IGOR - a public domain program for PCs - offers a wide variety of boundary conditions and restrictions for the user to choose from and to combine. The system is highly self-explanatory, and it enables the user to control the execution of the program in a transparent fashion. Complex chemical requirements and situations can be expressed in simple and clear terms. The results appear in a graphic representation as customary constitutional formulas that are familiar to chemists.

The *chemical horizon* of each run of IGOR is fixed by selecting, for each atomic site, a chemical element or a collection of chemical elements that may occupy this site. For each chemical element the allowable valence schemes and formal electrical charges are stated.

The user can express his chemical experience and imagination by a wide variety of optional restrictions, in order to guide the generating process.

The user can specify the values of the formal covalent bond orders between any two atoms. Requiring or forbidding certain substructures is very effective in the predetermination of the type of results. Substructures can be described to any degree of generality or detail in good/bad lists.

It is relatively easy to generate the constitutional formulas of a family of isomeric saturated hydrocarbons. There all atoms have fixed valence schemes and all nodes in the graphs of the molecules have constant degrees. However, as soon as more *chemical versatility* is introduced, e. g. multiple bonds, varying valence schemes and formal electrical charges, generating collections of chemical formulas according to specified requirements can become a formidable task, in particular when further chemistry-oriented conditions are imposed, like the required presence or absence of certain substructures.

Accordingly, the operation of IGOR requires a well-qualified chemist as a user. Then IGOR can be fine-tuned to produce results that are very close to chemical reality even when new chemical territories are explored.

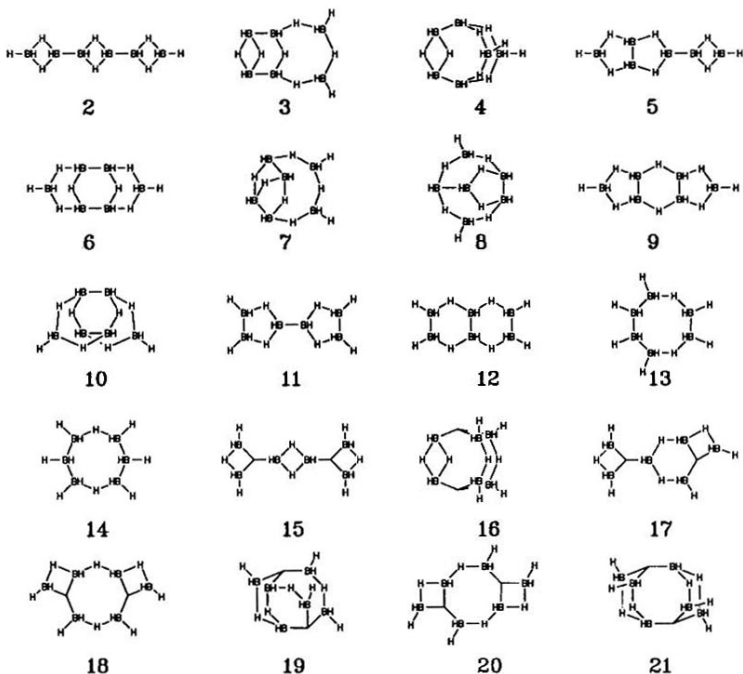
The following examples may illustrate the use of IGOR in the structure-generating mode:

With $(\text{CH})_8$ as the input the subfamily of cyclooctane and its 22 valence isomers results. In addition, IGOR can also be used to find out which of the latter valence isomers are interconvertible by a specified reaction mechanism.

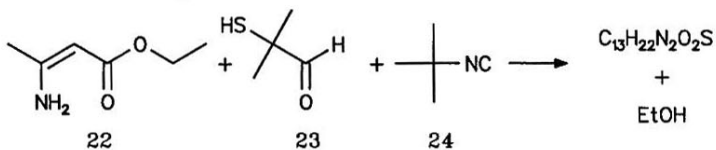
According to generation and enumeration by IGOR the $\text{C}_2\text{H}_2\text{N}_2\text{O}_2$ family contains 1806 isomers³² (no triple bonds or cumulated double bonds in rings; N may carry a formal "+" charge, N and O may carry "-" charges; overall electrically neutral), vs the seven isomers of C_4H_4 . When the $\text{C}_2\text{H}_2\text{N}_2\text{O}_2$ isomers are restricted to those that contain a five-membered ring, a subfamily of 52 isomers results³³.

In 1973, the research groups of F. Ramirez and I. Ugi began to jointly develop five-membered cyclic phosphorylating reagents for oligonucleotide syntheses⁵⁴. IGOR in the structure-generating mode played an important role in the final stages of this prolonged effort that at last ended successfully⁵⁵. IGOR generated 278 candidates from a suitably formulated definition of five-membered cyclic phosphorylating reagents⁵⁶. Six of these candidates were selected to be synthesized and tested⁵⁷. Finally, a few five-membered cyclic phosphorylating reagents were found that met all requirements⁵⁵.

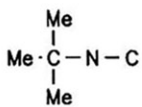
Due to its capability to respond to very detailed chemical specifications, IGOR shows great promise in automated structure elucidation. Here IGOR is



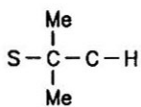
A compound with the empirical formula C₁₃H₂₂N₂O₂S is formed when ethyl-β-aminocrotonate **22**, α-mercaptoisobutyraldehyde **23** and tert.-butyl isocyanate **24** are subjected to certain conditions⁶⁰.



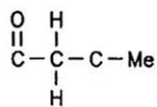
Under the assumption that **25** - **27** are the invariant substructures of the starting materials, the constitutional formulas **28** - **36** are the possible candidates for the product generated by RAIN 2.



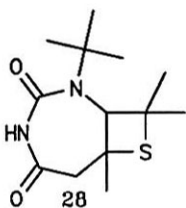
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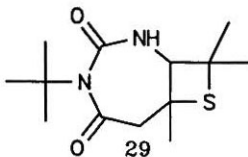
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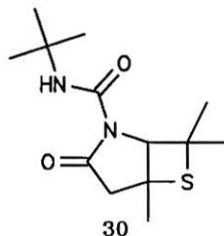
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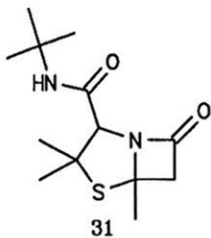
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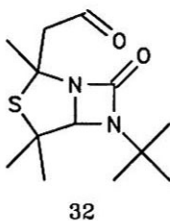
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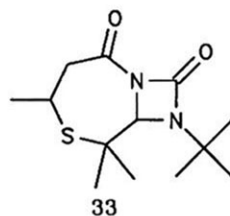
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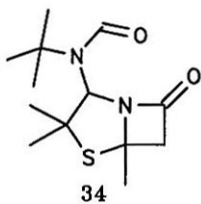
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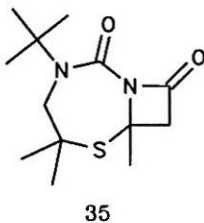
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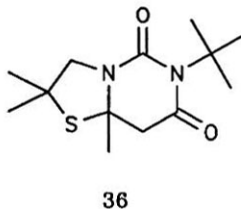
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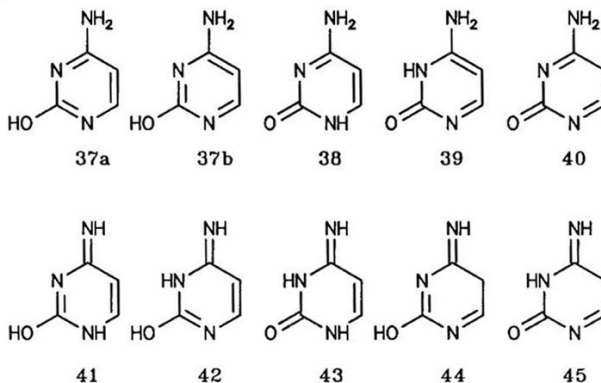


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RAIN 2 does not only generate a molecule, but also its resonance structures and its prototropic tautomers. When formal electric charges are forbidden, the resonance structures **37a** and **37b**, as well as the tautomers **38** - **45** are obtained for cytosine.



The computer-assisted elucidation of the chemical constitution of walbarganal⁶¹ is a very convincing application of GENOA⁴⁸. RAIN 2 and GENOA generate the same set of constitutional formulas from the empirical formula of walbarganal (C₁₅H₂₂NO₃) and a list of substructural constraints.

Conclusion

Mathematical chemistry will become more attractive and useful to chemists, if it provides devices and methods for solving the typical everyday problems of chemistry, and if the qualitative mathematical contributions to chemistry are explained more effectively than hitherto, so that chemists can immediately see their chemical applications. Particular attention should be devoted to the qualitative mathematical treatment of the dynamic aspect of the molecular reorganizations and redistributions of electrons that occur during isomerizations and chemical reactions. Often the time invariant properties of molecular systems are only of interest, because their knowledge is needed for the interpretation and prediction of the time-dependent changes of the considered systems.

In the future, theoretical chemistry, mathematical chemistry and computer chemistry are bound to be integrated into a unified discipline that will comprize

any conceptual and theoretical means for solving chemical problems, together with the corresponding algorithms and computer programs, providing new powerful tools for chemists.

Acknowledgements

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References

1. A. Cayley, *Phil. Mag.* **47**, 444 (1874).
2. J. J. Sylvester, *Nature* **17**, 284 (1877).
3. A. C. Lunn, J. K. Senior, *J. Phys. Chem.* **33**, 1027 (1929).
4. A. Pólya, *Acta Math.* **68**, 145 (1937).
5. P. K. Lindsay, B. G. Buchanan, E. A. Feigenbaum, J. Lederberg, "Applications of Artificial Intelligence for Organic Chemistry; The DENDRAL Project", Mc Graw-Hill, New York 1980.
6. N. A. B. Gray, "Computer-assisted Structure Elucidation", Wiley-Interscience, New York 1986.
7. A. Kerber, R. Laue, D. Moser, *Anal. Chim. Acta* **235**, 221 (1990).
8. A. T. Balaban, ed., "Chemical Applications of Graph Theory", Academic Press, London 1976.
9. E. Ruch, W. Hässelbarth, B. Richter: *Theoret. Chim. Acta* **19**, 288 (1970); W. Hässelbarth, E. Ruch, *Theoret. Chim. Acta* **29**, 259 (1973); W. Hässelbarth, E. Ruch, D. J. Klein, T. H. Seligman "Group Theoretical Methods in Physics", ed.: R. T. Sharp, B. Kolman, Academic Press, New York, p. 617.
10. N. G. De Bruijn, *Nieuw. Arch. Wiskunde* **18** (3), 61 (1970); A. Kerber, K.-J. Thürlings, "Symmetrieklassen von Funktionen und ihre Abzähltheorie", Bayreuther Mathematische Schriften, Bayreuth 1983.
11. I. Ugi, D. Marquarding, H. Klusacek, G. Gokel, P. Gillespie, *Angew. Chem.* **82**, 741(1970); *Angew. Chem. Int. Ed. Engl.* **9**, 703(1970).
12. I. Ugi, J. Dugundji, R. Kopp, D. Marquarding; "Perspectives in Theoretical Stereochemistry", Lecture Note Series, Bd. 36.; Springer, Heidelberg 1984.
13. R. S. Berry, *J. Chem. Phys.* **32**, 933 (1960).
14. P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, I. Ugi; *Angew. Chem.* **83**, 691(1971); *Angew. Chem. Int. Ed. Engl.* **10**, 687 (1971); I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie, F. Ramirez; *Accounts Chem. Res.* **4**, 288 (1971).
15. J. Brocas, M. Gielen, R. Willem, "The Permutational Approach to Dynamic Stereochemistry", Mc Graw- Hill, New York 1983.
16. M. Gielen, N. van Laetem, *Bull. Soc. Chim. Belges* **79**, 679 (1970); **80**, 207 (1971); J. I. Musher, *J. Am. Chem. Soc.* **94**, 5662 (1972); *Inorg. Chem.* **11**, 2335 (1972); *J. Chem. Educ.* **51**, 94 (1974).
17. E. P. Wigner, "Spectroscopic and Group Theoretical Methods in Physics" (Racah. Mem. Vol.), North Holland Publ. Co. Amsterdam 1971, p.131; *Proc. Roy. Soc. (London)* **A322**, 181 (1971).
18. R. Hoffmann, J. M. Howell, E. L. Muetterties, *J. Am. Chem. Soc.* **94**, 3047 (1972); R. R. Holmes, J. A. Deiters, *J. Am. Soc.* **99**, 3318 (1977); R. R. Holmes, *Acc. Chem. Res.* **12**, 257 (1979).
19. P. Lemmen, R. Baumgartner, I. Ugi, F. Ramirez, *Chemica Scripta* **28**, 451 (1988).
20. J. Dugundji, R. Kopp, D. Marquarding, I. Ugi, *Topics Curr. Chem.* **75**, 165 (1978).

21. J. Dugundji, D. Marquarding, I. Ugi, *Chemica Scripta* **9**, 74 (1976).
22. J. Dugundji, J. Showell, R. Kopp, D. Marquarding, I. Ugi, *Isr. J. Chem.* **20**, 20 (1980).
23. I. Ugi, M. Wochner, E. Fontain, J. Bauer, B. Gruber, R. Karl, in: "*Concepts and Applications of Chemical Similarity*", ed.: M. A. Johnson, G. M. Maggiora, John Wiley & Sons, Inc. New York 1990, p. 239.
24. I. Ugi, *Chimia* **40**, 340 (1986).
25. I. Ugi, B. Gruber, N. Stein, A. Demharter, *J. Chem. Inf. Comput. Sci.* **30**, 485-489 (1990).
26. J. Dugundji, I. Ugi, *Top. Curr. Chem.* **39**, 19-64 (1973); I. Ugi, *J. Indian. Chem. Soc.* **62**, 864 (1985); in: "*Computers in Chemical Research and Education*", Herausg.: J. Brandt, I. Ugi, Hüthig Verlag, Stuttgart 1989, p. 345.
27. J. Brandt, J. Bauer, R. M. Frank, A. v. Scholley, *Chem. Scr.* **18**, 53 (1981).
28. J. Koca, M. Kratochvil, L. Matyska, J. Pospichal, V. Kvasnicka, "*Synthon Model of Organic Chemistry and Synthesis Design*", Lecture Note Ser. 51, Springer, Heidelberg 1989.
29. J. Bauer, I. Ugi, *J. Chem. Res.* **1982**, (S) 298; (M) 3101; J. Bauer, Doctoral Thesis, Technische Universität München 1981.
30. J. Bauer, R. Herges, E. Fontain, I. Ugi, *Chimia* **39**, 43 (1985).
31. J. Bauer, *Tetrahedron Comput. Methodol.* **2**, 269 (1989).
32. I. Ugi, J. Bauer, K. Bley, A. Dengler, A. Dietz, E. Fontain, B. Gruber, M. Knauer, K. Reitsam, N. Stein, *Angew. Chem.*, submitted.
33. I. Ugi, J. Bauer, E. Fontain, in: "*Personal Computers for Chemists*", ed.: J. Zupan, Elsevier, Amsterdam 1990, p.135.
34. E. Fontain, K. Reitsam, *J. Chem. Inform. Comput. Sci.* **31**, 96 (1991).
35. E. Fontain, J. Bauer, I. Ugi, *Chem. Letters* **1987**, 37; E. Fontain, J. Bauer, I. Ugi, *Z. Naturforsch.* **42B**, 889(1987).
36. E. Fontain, *Tetrahedron Comput. Methodol.*, in press.
37. I. Ugi, J. Bauer, E. Fontain, *Anal. Chim. Acta* **235**, 155 (1990).
38. I. Ugi, J. Bauer, K. Bley, A. Dengler, A. Dietz, E. Fontain, B. Gruber, M. Knauer, K. Reitsam, N. Stein, *Labor Praxis* **1991**, 170.
39. K. Bley, B. Gruber, M. Knauer, N. Stein, I. Ugi, R. Weidinger, *Top. Curr. Chem.*, in press.
40. H. L. Morgan, *J. Chem. Doc.* **5**, 107 (1965).
41. W. Schubert, I. Ugi, *J. Am. Chem. Soc.* **100**, 37-41 (1978); *Chimia* **33**, 183 (1979); see also : J. Blair, J. Gasteiger, C. Gillespie, P. D. Gillespie, I. Ugi, *Tetrahedron* **30**, 1845 (1974); J. Gasteiger, P. D. Gillespie, D. Marquarding, I. Ugi, *Topics Curr. Chem.* **48**, 1(1974).
42. R. S. Cahn, C. K. Ingold, *J. Chem. Soc.* **1951**, 612; R. S. Cahn, C. K. Ingold, V. Prelog, *Experientia* **12**, 81 (1956); *Angew. Chem.* **78**, 413 (1966); *Angew. Chem. Int. Ed. Engl.* **5**, (1966); V. Prelog, G. Helmchen, *Angew. Chem.* **94**, 614 (1982); *Angew. Chem. Int. Ed. Engl.* **21**, 567 (1982).
44. J. Lederberg, *Proc. Nat. Acad. Sci. (USA)*, **53**, 134 (1965).
45. L. A. Gribov, M. E. Elyashberg, *J. Molec. Struct. (Theochem)* **5**, 179 (1970)
46. S. I. Sasaki, H. Abe, T. Ouki, M. Sakamoto, S. Ochiai, *Anal. Chem.* **40**, 2220 (1986).
47. R. E. Carhart, D. H. Smith, H. Brown, C. Djerassi, *J. Am. Chem. Soc.* **97**, 5755 (1975).
48. R. E. Carhart, D. H. Smith, N. A. B. Gray, J. G. Nourse, C. Djerassi, *J. Org. Chem.* **46**, 1708 (1981).
49. Y. Kudo, S. Sasaki, *J. Chem. Inf. Comput. Sci.* **16**, 43 (1976); S. Sasaki, H. Abe, Y. Hiroka, Y. Ishida, Y. Kudo, S. Ochiai, K. Saito, T. Yamasaki, *ibid.* **18**, (1978).
50. C. A. Shelley, T. R. Hays, M. E. Munk, R. V. Roman, *Anal. Chim. Acta* **103**, 121 (1978); C. A. Shelley, M. E. Munk, *ibid.* **133**, 507 (1981); C. A. Shelley, H. B. Woodruff, C. R. Snelling, M. E. Munk, in (D. H. Smith, ed.): "*Computer-assisted Structure Elucidation*", ACS, Washington DC 1977, 92, Ch. 7.
51. V. V. Serov, M. E. Eliashberg, L. A. Gribov, *Anal. Chim. Acta* **95**, 75 (1977); *J. Mol. Struct. (Theochem)* **31**, 381 (1981).
52. B. Debska, J. Duliban, B. Guzowska-Swider, Z. Hippe, *Anal. Chem. Acta* **133**, 303 (1981).

53. J. B. Hendrickson, C. A. Parks, *J. Chem. Inf. Comput. Sci.* **31**, 96 (1991); C. A. Paulus, J. B. Hendrickson, *ibid.* **31**, 334 (1991).
54. F. Ramirez, S. Glaser, P. Stern, P. D. Gillespie, I. Ugi, *Angew. Chem.* **85**, 39 (1973), *Angew. Chem. Int. Ed. Engl.* **12**, 66 (1973).
55. W. Richter, R. Karl, I. Ugi, *Tetrahedron* **46**, 3167(1990); W. Richter, I. Ugi, *Synthesis* **1990**, 661; P. Jacob, W. Richter, I. Ugi, *Liebigs Ann. Chem.* **1991**, 519.
56. I. Ugi, J. Bauer, E. Fontain, J. Götz, G. Hering, P. Jacob, B. Landgraf, R. Karl, P. Lemmen, R. Schneiderwind-Stöcklein, R. Schwarz, P. Sluka, N. Balgobin, J. Chattopadhyaya, T. Pathak, X.-X. Zhou, *Chemica Scripta* **26**, 205 (1986).
57. I. Ugi, N. Bachmeier, R. Herrmann, P. Jacob, R. Karl, M. Klein, P. Lemmen, W. Richter, U. Verfürth, *Phosphorus Sulfur & Silicon* **51/52**, 57 (1990).
58. W. N. Lipscomb, "*Boron Hydrides*", Benjamin, New York 1966, p. 57.
59. B. Brellochs, H. Binder, *Angew. Chem.* **100**, 270 (1988); *Angew. Chem. Int. Ed. Engl.* **27**, 262 (1988); H. Binder, B. Brellochs, B. Frei, A. Simon, B. Hettich, *Chem. Ber.* **122**, 1049 (1989).
60. I. Ugi, E. Wischhöfer, *Chem. Ber.* **95**, 136 (1962).
61. Chapter II of ref. 6.