Computer Chemistry

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To My Mother
and the KL Eagles

PREFACE

In the last decade we have witnessed a blooming activity in the field of computer applications in chemistry. The reason for this wide acceptance of computer methodologies among chemists may be seen in the particular structure of chemical problems, which can be easily recognized as having strong combinatorial features. It is well known that such problems often resemble solving puzzles in which each stone must be located in one, and only one, proper place to yield a correct final picture. The same happens in chemistry when trying to assemble molecular "fragments", the substructures derived from visual interpretation of spectral data, to form a complete molecule. Similarly, the mental dissection of a molecular structure usually performed by the synthetic chemist to conceive possible synthesis routes is one more classic example where the human brain must tackle monumental combinatorial and permutatorial problems. It was these two main branches of chemical research that stimulated, at the beginning of the 1970s, the birth of the first attempts to combine artificial intelligence and chemistry. We could say that computer chemistry originated in the wish to emulate human chemical thinking within a computer. For this reason, as explained in great depth in the text, computer chemistry must not be regarded as computational chemistry, which is primarily dominated by quantum chemistry. This fact is demonstrated by the history of computer chemistry and its pioneers, the majority of whom were organic chemists. This proves that it was the attempt to reproduce chemical "thinking", and not chemical "computing", that provided the driving force in the primary efforts to compile chemically intelligent computer programs.

The first important schools of computer chemistry were found in illustrious universities in the U.S., Germany, and Japan; this young science had a merely academic character, and many observers just shrugged their shoulders when hearing about "synthesis design programs" or "autodeductive structure elucidation programs". They were somehow annoyed by the possibility that a computer could "think". Computer chemists were considered daydreamers, chemistry hippies not worthy of any serious consideration.

However, the importance of computer chemistry was soon recognized by chemical industry. Its intrinsic potential to enhance laboratory performance was readily made evident, and since then a great deal of funds have been invested for large-scale computerization of industrial chemical research, both in software and hardware.

These last years have definitely seen computer chemistry being accepted even among its previous opponents. Teaching courses are held today in many universities around the world. Learning programming languages has become customary among many chemistry students.

It is further interesting to note how the necessary formulation of chemistry by means of algorithms has been reflected in a clearer view of our conceptual chemical models. The advent of extremely fast computers has cleared the way for the treatment of chemical problems of a complexity unthinkable just 5 years ago. Protein modeling and retrieval of chemical information from data bases containing millions of structural data also have become feasible due to dramatic improvements in hardware architecture. Parallel processors are introducing a revolution in chemical software design and application. Tabletop supercomputers will be available soon, and what appears to be impracticable today will be obvious in a few years. Computer chemistry is evolving at such a speed that any book can seem obsolete if it has to report about the technology. For this reason, this volume is aimed at a conceptual and even philosophical presentation of computer chemistry, enhancing its peculiar psychological aspects; the author has attempted to focus its description on how our human knowledge of chemistry can be transformed into formal schemes, the chemical rules, and then expressed in a form that makes their representation in a computer program possible. This volume is therefore neither a collection of descriptions of the most important computer chemistry

software packages nor the exaltation of some specific programs described in more detail than others. It merely attempts to introduce the graduate student, the industrial chemist, the analytical chemist, and the pharmacologist to the world of computer methods in chemical research, which are not alternative but complementary to the currently adopted tools of investigation.

The author has spent more time on the explanation of specific software systems on which he has worked or which he has used frequently. This does not mean that these systems are superior to others that are only cited here: no quality ranking is given for any achievement whatsoever, and judgments are limited strictly to chemical and technical characterizations of the introduced software systems. This book also does not subsititute more specific original literature, but tries to act as a primer for the student approaching computer-assisted methods in chemical research.

Mario Marsili
Rome, Italy
April 1989

THE AUTHOR

Mario Marsili, Ph.D., was born in Rome in 1953. He left his home country at the age of 18 to study chemistry at the Technical University, Munich, Federal Republic of Germany. In 1977 he obtained the "Diplom" degree in chemistry with research work on fast algorithms for the computation of partial atomic charges in molecules based on orbital electronegativity. He earned his Ph.D. at the Technical University 3 years later in the area of computer-assisted synthesis design, where he had expanded the charge calculational models to pi electron systems and first derived bond reactivity functions to be utilized as "deductive" means inside of the synthesis design program EROS, the development of which he contributed to under the leadership of Professor Gasteiger.

He spent one postdoctoral year at the University of Zurich in Switzerland with Professor A. Dreiding, where he worked in the area of molecular graphics and molecular modeling, creating a computerized method for morphological comparison of three-dimensional molecular structures. In 1982 he was appointed Lecturer in Computer Chemistry at the University of Zurich. At the end of 1982 he was called back to Italy by the National Research Council of Italy and joined the team of the Project on Fine Chemistry, directed by Professor L. Caglioti; there he established the first Italian Computer Chemistry research unit. In 1985 he was nominated Assistant Professor of Computer Chemistry at the Rome University "La Sapienza", where he stayed for 3 years. In 1986 he was elected Director of the Strategic Project on Computer Chemistry inside of the National Research Council. At the same time, Italian industry took up the challenge in computer chemistry and an important research project was launched, supported jointly by the Istituto Mobiliare Italiano and 15 Italian chemical and pharmaceutical industries. The project, carried out in the Tecnofarmaci laboratories, was led by Mario Marsili for the scheduled 4 years, ending in the creation of a global molecular modeling system, SUPERNOVA. Currently, he is Professor of Computer Chemistry at the University of L'Aquila and team leader of several industrial research projects in Italy, Germany, and Japan. His actual major fields of interest are molecular modeling and chemometrics.

Dr. Marsili is the author of more than 30 original papers in computer chemistry. He was President of the Ninth International Conference on Computers in Chemical Research and Education, held in Italy in May 1989.

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INTRODUCTION

I. MAN AND COMPUTERS

Computers have entered most areas of scientific research, industrial production, and educational activities to such an extent that an impact has even been made on the social life, mental attitude, and the psychology of people. Computers can often replace or support many human activities at low costs: cars are assembled by robots; teachers are substituted by computer programs, experienced instructors by simulators. This has occurred because computers are millions of times faster than man. Speed is the name of the game, and speed means competitiveness on the market, low financial investments, and better overall performance. On the other hand, a certain number of disappearing human activities, obsolete and no longer considered profitable, are transformed into new equivalents under a different perspective: the computer perspective. Somebody who in the past manufactured coil springs for wristwatches is almost no longer required, having been replaced by somebody constructing the integrated circuits on which modern watches rely.

Computers have disclosed new frontiers in medicine, improving diagnostic techniques (e.g., imaging in computerized axial tomography). They have caused a real revolution in data management and communication and allow modeling of extremely sophisticated systems like astrophysical events or weather forecasts.

Computers undoubtedly provide a number of astonishing improvements in several sectors of the modern world, but are at the same time the backbone of modern warfare, which has created the most incredible array of annihilating weapons ever (pattern-recognizing "intelligent" missiles, for example). For the single human, this double-faced process of technological evolution has bloomed into a wealth of new professions, all of them connected to computer science, be it theoretical or applied.

Computers are neither good or bad; a knife is neither good nor bad. Each depends on its use. Philosophical fights are raging everywhere on the role of man in a computer-dominated world in which few selected specialists have the knowledge and the power to press strategic buttons on keyboards, and no final solution is expected soon. The question whether human intuition (in other words, the artistic gift, the invention, the intellectual breakthrough) can be replaced by computer simulation, once computers have enough memory and speed to tackle such problems, is indeed a central question and contains even a touch of moral texture.

If a computer simulation based on artificial intelligence systems leads to some unexpected brilliant scientific discovery, is this the merit of the human programmer or of the "thinking" computer?

Chemistry is no exception within the framework of this discussion. The introduction of computer-assisted research techniques into chemistry over the last 15 years has caused a split pattern of reactions among chemists. Whenever computers have been used in a kind of subordinate, secondary, concealed way, they have been accepted as precious and powerful help. This has especially been the case with regard to chemical information and in analytical chemistry. On the contrary, as soon as computers entered an apparent role of equality with the human chemist in solving problems of a more decisional type, exerting a primary, direct influence on man-tailored research strategies and methods, an evident anxiety arose among traditional-minded chemists. Chemists saw (and still see) their leading role as "masters of the art" endangered by an "idiot made of steel". Grown on a serious misunderstanding of the role of computers in chemistry, this attitude in some cases has led to mental rejection of this new technology at the level of its cultural root. On the other hand, enthusiasts are

readily found who expect immediate successful results to a variety of difficult problems, believing that "the computer can do everything." They forget that computers still depend primarily on man's performance.

To understand the reasons for a methodology called computer chemistry, to correctly place it among modern research methods, and to detect its benefits and limitations — these points must be discussed in some depth.

II. COMPUTERS IN CHEMISTRY

A. COMPUTATIONAL PROGRAMS

A distinction was postulated above between a direct, or primary, influence of computer action on chemical research and a subordinate, secondary one. Historically this distinction, caused by an independent growth of what is called computer chemistry from other traditional fields of computer applications in chemistry, was rooted in two main facts: the attempt to create computer programs to emulate chemical thinking, and the parallel development of a new, fascinating, and promising branch of computer science, artificial intelligence (AI). AI, which will be discussed later to some extent, is the part of computer science dealing with the computer-generated perception and solution of complex symbol-oriented and semantic problems.

In the early 1970s, chemists were acquainted with a purely numerical use of computers in chemistry. Quantum chemistry and X-ray structure determination were the poles of heaviest exploitation of the fast computational capacity of a computer. In both of these important research fields, the investigator faces such an enormous quantity of bare numbers that their successful treatment would be utterly unfeasible without electronic data processing. The main role of computers in performing these tasks simply consists of managing huge arrays of numbers following a user-implemented, rigid, predetermined prescription. The result of what in a joking manner is termed "number crunching" is in all of these situations a mere numerical result. In other words, the computer delivers a certain number of specific magnitude that interests the user, and the path along which such a number is generated is a one-way road within the codified program. Solving iteratively thousands of Coulomb or exchange integrals and refining Fourier coefficients are examples of such a path. Here the computer follows a fixed scheme of data processing. The final result, for example, could be the energy of some specific electronic state of a given molecule or an array of cartesian coordinates for atoms in a molecule. That is what we expect. The magnitudes of energy and coordinates will change if the investigated substrate is different, but this is obvious. They will also change if a different degree of approximation, refinement, or parameterization is chosen by the user. What does not change is the certainty that some number will come out as the unique result. We might not known in advance what energy value a certain molecule will show at its conformational minimum, but that is the main reason for using a computer: to do the necessary calculations according to user-determined equations which already contain the solution to the problem in all its principles. Due to its advantage in speed, the computer offers a numerical result for final interpretation by man. The program run by the computer contains no alternatives other than to produce quantitative numerical answers of one and the same kind, repetitively, as it has been instructed to do. Truly, there are no alternatives to atomic coordinates for a program that calculates atomic coordinates. The statement "I shall ask the computer to tell me the energy of formation of this molecule" appears to be conceptually and semantically wrong. Justified questioning anticipates the potential existence of an answer; answering demands the *a priori* existence of choice elements among which a suitable answer can be found.

A quantum mechanical program, once implemented according to a particular approach, is geared in a way as to solely calculate a set of numerical quantities, and it has no choice

elements on which to exert any kind of deductive evaluation for constructing an answer. Thus, the actual calculation is just a reproduction of the equations contained in the program, substituting real numbers for symbols: no influence is exerted by the computer on the strategic content of the program, on its structure, or on its meaning, and the computer will not be able to change the structures of the equations themselves during execution. Question and answer are like vectors: each has a magnitude *and* a direction in space. The direction determines the difference between a vector and a scalar. Selecting a direction (i.e., including deduction in the formulation of a certain answer by considering the nature of the available choice elements) means adding a qualitative element to a purely quantitative response. Calculating orbital energies cannot produce chemical answers within the conceptual framework just expounded because programs tackling these kinds of computational problems yield scalar numbers (e.g., energies) as results. The direction that we miss in such results, which is nothing less than the general structure of the solution scheme, is called the solution model. In lucky cases of a known theory, this direction is known in advance by the investigator and formulated as a sequence of instructions in a computer program. We can finally assert the following:

Assertion I — *Computational programs in chemistry rely on predefined solution schemes, the models, which are known in their qualitative essence by the user. The output of such programs is a quantitative response, a scalar, for the model under specific, user-given conditions. The generation of such responses follows a rigid, unbranched, and constant data processing mechanism. No strategy evaluation is involved.*

It clearly now appears that computer support in this fashion does not scratch the polished image of any scientist devoting his time to the discovery of fundamental theories or models. He remains master of the situation and welcomes computer aid as a fast and reliable processor of numbers in a kind of subordinate position. In final words, the computer will not teach him anything.

B. SEMANTIC PROGRAMS

What would happen to human psychology and to scientific research if a computer started to deliver qualitative answers, to give strategic advice, to propose models, to change the structure of user input equations, or to emulate chemical reasoning?

To do this, a computer perception of quality must be created. Quality involves comparison; comparison involves rules for judgment; using rules involves the capacity of autonomous acting; acting involves effects; effects involve interpretation and ranking, which finally contribute to the establishment of quality. Quality and quantity together build our response vector, the answer.

Computer chemistry started off right at this point: it provided programs, along with the first blooming achievements and concepts in AI, that were able to help chemists discover strategies. These programs had to be organized flexibly enough to deal with varying mechanisms for making choices. This key term requires the questions addressed to the computer to have, in principle, a manifold set of possible outcomes, which undergo evaluation and ranking.

The intrinsically different response vectors may differ in probability (the magnitude of the vector) and in direction (the quality, the conceptual content of the computer-generated solution, the strategic orientation). Such programs are well suited, in general terms, to provide alternative models, thus enhancing knowledge. That is exactly the complementary (not the opposite) situation to computational programs. The latter apply established models, while the former use general rules (empirical or theoretical), to produce models and ranking strategies. For example, calculating the energy in calories that one needs to move one's arm while playing chess (i.e., to pick up a piece, move it to its new position, and lower the arm again) corresponds to the use of a program belonging to the computational class. However,

asking the computer that has been "taught" chess rules to predict all possible sequences of moves leading to checkmate, starting from a user-given initial pattern, is an example of the use of programs of the AI class. Here the process of establishing strategies, predicting countermoves, and ranking sequences of moves according to chance of success is the principal feature of such an autodeductive program.

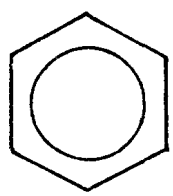
In computer chemistry, chemical rules are transformed into a program inside a computer, making the electronic device look like it is thinking chemically and therefore turning it into a seeming threat, a cold, stainless steel rival of any human chemist. Computer answers of the following kind are common today, and they make the instinctive repulsion among a few, if not justifiable, at least comprehensible; for example, "Your mass spectrum belongs with 96% probability to a molecule with three chlorine atoms," or "There are 24 different reaction routes within an exothermic range of 0 to 10 kcal/mol that can lead to your desired product; I will draw them for you," or "After interpreting all your spectral data, three molecular structures were found compatible and were generated; here they are," or "You don't have to care for the temperature parameter while running your chemical reactor; adjust the pH to 5.5 instead."

These answers clearly go far beyond those to which chemists had been typically accustomed. They offer direct intervention into operational strategy, as well as tactical realization. They lead to a redesign of a certain experimental setup or to a new, unexpected conceptual insight. Thus, a revised model can be developed. We finally can assert the following:

Assertion II — *Semantic programs are the core of computer chemistry systems. They are tailored to reproduce schemes of human reasoning — in our case, of chemical thinking. They use chemical rules to treat the strategic, decisional kind of problem. They have a primary influence on subsequent methodologies, the establishment of models, the creation of alternatives, and the intelligent interpretation of data in chemical research.*

C. COMPUTER CHEMISTRY AND HUMAN PSYCHOLOGY

The first accomplishment that must be fulfilled is the computer perception and recognition of chemical symbols. Our whole comprehension of chemistry is based on a reiterate confluence of symbols and their chemical content in the human brain, where they are perceived and stored. This process, which takes place over all the years of apprenticeship in chemistry, establishes an automatism that elicits all our chemical knowledge if a visual or phonetic stimulation is conveyed to our cerebral chemical data base. For example, if someone is told the word "benzene", he most likely will visualize in his mind the familiar pictorial symbol for benzene; however, at the same time he will subconsciously correlate to it a number of specific features that he knows are hidden somewhat cryptically in the depiction which certainly belong to benzene as a real chemical entity.



The benzene symbol automatically includes the six hydrogen atoms not drawn explicitly, and the ring inside the hexagon is immediately understood as symbolizing six delocalized π electrons. Even the concept of delocalization is recalled in the brain and is readily formulated as a $(4n + 2)\pi$-electron Hückel rule. This happens at an astonishingly high speed in the human mind. The reason for it is that symbols and their correlated chemical

and physical properties are already stored in the brain; they represent our chemical knowledge base. Recalling chemical data (retrieving structural formulas) is a procedure that we do every day while discussing chemistry. A computer does very similar work when used for chemical data retrieval, one of the first applications of computer technology in chemistry. Conceptually, data retrieval is remotely connected to semantic programming, as it generally deals with the matching of input character strings (the name of a molecule, for example) with corresponding strings inside the data base. A relation to truly semantic systems is to be found just in the ability of modern retrieval systems to accept symbols as input, to perform sophisticated logical search and matching operations, and to return the results in an equally sophisticated, symbol-oriented manner. However, no additional original material is generated by the computer during a search session. Autogenous creation of something new must occur by different paths, both in the brain and in computers. Searching for a chemical structure in an array of collected structures stored on some magnetic device can have only one of two possible outcomes: found or not found. In the "not found" situation, the computer cannot augment the data base with the one missing datum because it does not "know" it until an operator supplies the new entry. The unquestionable usefulness of data banks is exemplified by the evident speed in gathering available data as compared to man. The simple psychological experiment of visualizing the benzene symbol and automatically attaching to it all of the chemistry we know (from learning and from practice) highlights the parallelism of our power of perception, our memory, and our retrieving and correlative capabilities with the computer equivalents. These are engineered and emulated inside specific software and deal with a finite set of known elements.

We shall continue this psychological investigation, shifting to problems where new, still unknown elements must be deductively inferred and linked to the previous set. The following argument is an an example of the many possible paradigmatic representations focusing on giving evidence to the differences between man and computer in autogenous creation and manipulation of symbolic elements. It justifies the consistency of inclusion of computer chemistry tools in modern chemical research.

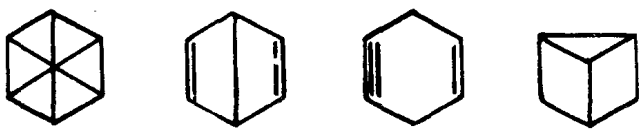
Let us use a different symbol for the representation of benzene, which now will be C_6H_6. This tells us that six carbon and six hydrogen atoms, connected through chemical bonds, form what we call a molecule. Now, in this fictitious experiment, the problem put both to man and computer is to generate all possible structures with the given set of atoms (i.e., generate all isomers of benzene).

The problem is of a semantic/symbol-oriented nature, and according to assertion II its solution requires a number of rules to build the skeleton of the AI procedure. Organic chemistry supplies the rules.

Rule 1. A carbon atom must have four bonds, regardless of its arrangement with connecting partners.
Rule 2. Each hydrogen atom must have one bond connecting it to the next partner.
Rule 3. The molecules must be in a neutral state.
Rule 4. Structures obeying Rules 1 and 2 are valid whether or not they are thermodynamically stable.
Rule 5. No disconnected atoms are allowed.

Disposing of the rules, one can attack the problem of generating as many topological isomers of benzene as possible. Looking at benzene, our fantasy involves the search for a new arrangement of the graphical elements (the lines representing bonds) that constitute the pieces of the game (consider, for example, the analogy to a chess game). The first attempt likely would be to transpose the "localized" double bonds to obtain a new image, as in the case of Dewar benzene (structure b below). Another scheme of bond shifting leads to the

symmetrical structure **a**, while structure **c**, retaining a hexagonal pattern of carbon atoms, shows one triple and one double bond, with two carbons having more than one hydrogen. If structures **a** and **b** needed only the rearrangement of lines corresponding to double bonds, structure **c** would involve the regrouping of atoms. A major mental combinatoric effort is necessary in abandoning the familiar six-membered ring, which somehow influences inventive flexibility: in the chemist's mind, the hexagon correlates to a flat molecule, a two-dimensional structure. Exploding the 12 available atoms into three dimensions beams to the beautiful structure **d**, *prismane*.



a b c d

Sooner or later, man's intuition will lead to other images, like open-chain compounds or isomers with five- or four-membered rings in them. The reader may wish to exert himself by finding other elements in the finite set of benzene isomers.

A major difficulty arises when a certain number of isomers have been derived by hand. Suppose that 35 different isomers have been drawn on paper. A 36th is born in the chemist's mind, and in order to validate it he will have to compare the new structure with the other 35. As the mind cannot keep track of so many different images simultaneously, and as they are not perceived and stored in a unique, canonical way, the chemist will in many cases find that the 36th isomer is one that he has generated already. As an example, he might have deduced as the 36th isomer the following open-chain structure,

$$H\text{–}C{\equiv}C\text{–}CH{=}CH\text{–}CH{=}CH_2$$

and, going back through a one-by-one structural check, realized that it is the same as

$$CH_2{=}CH\text{–}CH{=}CH\text{–}C{\equiv}C\text{–}H$$

which he had found long before. The reason is that his mind works on images (symbols), which are remembered not in their abstract, intrinsic nature, but simply as they have been perceived visually; thus, the first linear code given above, once reflected, is at first judged as a different molecule. The brain is not trained for immediate recognition of asymmetrical structures.

The reader interested in knowing how many different structures can be assembled from C_6H_6 and who does not wish to spend the next 6 months doing it without computer help can find them all in the Appendix at the end of this volume. This task takes only a few seconds on a modern mainframe computer.

The human mind seems to be the very best instrument for conceptual breakthroughs, but reveals slowness in exhaustive solution of combinatorial problems. Can the speed at which a computer performs operations be a masked kind of intuition? The great steps in intellectual achievement in man's history were obtained by intuition and not by fast treatment of data according to known rules, as was the case with the benzene isomers. Going from the geocentric concept of the world of the Middle Ages to a heliocentric concept, recognizing the four dimensions of space-time with time being no more absolute, and conceiving particles as waves and waves as particles are examples of the sublime flower of pure intuition, which *breaks rules!* Breaking rules is only in the realm of human thought. Our chemical example proved valuable in understanding the power of a computer in managing data according to

rules, but no computer could have such a complete perception of any complex system that it could invent new fundamental rules and, thus, change the boundaries of validity of our rules. This is left to man.

We are now able to confine the role of computers to a well-determined region in chemical research. The computational use of computers requires data to produce data; the use according to AI concepts takes data and rules to produce information, and our minds use intuition to interpret information to finally produce knowledge.

The path between data and information is the area of application of computer chemistry programs.

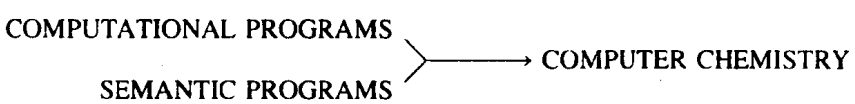
To end our philosophical digression, we could say that the proper use of knowledge produces wisdom, but this still seems a distant goal for mankind.

Computers can then be instructed to deal with chemical problems where the following hurdles appear to burden human efficiency:

1. An intrinsic difficulty in going from an element n to the next element, $n + 1$, in combinatoric work
2. The creative mind being stained by memories, which are constantly interfering with the new, unborn images we try to bring forth
3. The impossibility of canonical recording of complex structures
4. Danger of redundancy in creation
5. Lack of means to establish the completeness of a finite set of generated elements for a complex system

The reason why computer chemistry diverged from classical computer applications in chemistry (quantum chemistry, physical chemistry, chemical kinetics, X-ray analysis, etc.) and separate journals and conferences were established is rooted in the necessity to deal with formal problems regarding the symbolic perception of molecular structure by computers. Many years were spent generating programs for the perception of rings and aromaticity, for the canonical numbering of atoms in a molecule, for effective user-friendly input and output interfaces, for the recognition and storage of particular substructural features, for the encoding of reaction schemes in reaction data bases, for the fast and compact storage and retrieval of molecular structures, and for the codification of chemical rules. Later, when these basic problems were obliterated, a shift toward a more refined introduction of physicochemical parameters into semantic models, enhancing the chemical quality of computer simulations, took place. Today, due to the enormous speed of mainframe computers (some of them array processors), a greater use of computationally oriented software to feed the semantic, AI-oriented systems with the necessary, more sophisticated data is becoming increasingly popular.

The present stages of evolution show computer chemistry as an established research area constantly propelled by two major mutually supporting thrusts: semantic programs and computational programs.



III. AREAS OF APPLICATION OF COMPUTER CHEMISTRY METHODS

Imagine an analytical chemist isolating some particular pharmacologically interesting molecule from an animal or plant system and attempting to elucidate its chemical structure. He will use all available modern analytical tools (e.g., high-performance liquid chromatography [HPLC], gas chromatography/mass spectroscopy [GC/MS], infrared spectroscopy