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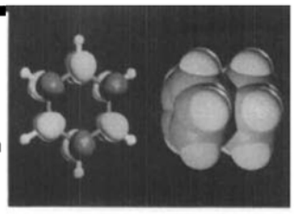

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Molecular Modeling – Still Going Strong

Once upon a time in the early seventies of the twentieth century the Club of Rome published a book called the 'Limits of Growth'. The authors described a world model, *i.e.* they tried to condense the main factors which are supposed to determine the future of the world and the human race into a mathematical model and so compute likely future scenarios. There was a broad controversy among the people who read the book (and also among the ones who did not read it) about the significance of such a model. A decade later the fight was over. Here and there you could hear a lonely politician pointing out that the predictions as everybody could see had not turned out as expected!

Once upon a time in the sixties of the twentieth century some chemists published papers about 'Molecular Modeling'. The authors described mathematical models which were implemented in computer programs so as to calculate molecular properties and to generate beautiful coloured pictures. There was a broad controversy among the people who read the papers (and also among the ones who did not read them) about the significance of such models. A decade later the fight was over. Here and there ...

What do these two examples have in common? In both cases they took off in a spectacular way with headlines in the news. In both cases the 'ones who did not read' saw only the results and were possibly enthusiastic about them at the beginning, but disappointed later on when the scenarios turned out not to be true. However, the 'ones who read' could see more than just the results, more than an impressive computer program, they saw it as a new conception. The results are of less importance to them than the road leading there. You can see it as a new approach of science: to investigate complex systems which were previously not amenable to a mathematical approach, and were, thus, left to speculation. The fight is not over, but it is no longer in the headlines.

The 'world models' no longer give inaccurate predictions for the development of the whole human race. But a lot of research now goes on in economics, in communication science and in ecological science to develop models along that line. They have less ambitious goals, but have reached much higher accuracy, and they have a whole philosophy which can make them building blocks for a step toward the 'world model'.

Similarly, molecular modeling turns out to be rather a conception which shows us the road to the simulation of complex chemical systems in the future. Only a few building blocks are yet available. Their performance is still subject to improvement. But we are on the way!

I. Graphics

A first building block is the computerized description of molecules, leading to different graphics models illustrating the various aspects of molecular structure. Progress has been made since the 'early years' by utilizing interactive computer graphics facilities and fast, cheap, up-to-date hardware. Nevertheless the question remains: what is the advantage compared to the classical molecule construction kit?

Nobody will urge the student to use a million dollar computer to replace the construction kit. However, for professional use computer modeling has some clear advantages. Have you ever tried to build a protein with a fifty dollar kit? Not only are you limited with the 50 atoms you find in your box, but also the handling may be somewhat problematic. At the beginning you may do well with your five hands but when you want to investigate a second conformation you can hear your bones creak.

How much easier is it on the computer? You build up your molecule from fragments just by drawing, clicking the mouse-button and choosing some menus. You zoom in and out of your molecule. You move and turn your model by a key-press. You perform internal rotations around any bond by choosing the bond with your mouse. But in addition you can extract the whole information the computer has about your molecule, *e.g.* any distance between atoms, valence and torsion angles. You can even monitor in real time the distance between atoms which are close to one another while you are turning around a bond. This is already going far beyond what you can expect from your model kit. Even the price advantage of the kit is decreasing as personal computers become a desktop accessory, replacing pen and eraser.

But we should not forget the main point: the graphics and mathematical representation in the computer is only the first building block of a philosophy going far beyond that. A second block is already well developed as molecular mechanics.

II. Molecular Mechanics

Molecular mechanics or force-field calculations are used today in most molecular modeling programs to improve the rough structure obtained from the input step. The input program usually applies similar rules as they are used in construction kits, *e.g.* a fixed angle of 109.5° at an sp^3-hybrized carbon atom. Let us give a simple example for the beginner, to explain how molecular mechanics works.

Assume you wish to optimize the structure of the CO molecule. A typical program allows you to make a graphical input by drawing the bond from one atom to the other and marking the atoms as C an O, respectively. In addition the program contains a mechanical model of the bond stretching potential. In this case, this could be a harmonic assumption for the stretch energy E_s:

$$E_s = c_1(r - r_0)^2$$

The program contains in large tables parameters like r_0 and c_1 for all different pairs of atoms which can be handled. The actual bond-length r is given by your input. Hence, the program can calculate the (relative) energy of your molecule. Having done that it will change the bond-length slightly in a systematic way such that the energy will become lower and lower and finally will reach a minimum. Then it has reached the stable structure of the molecule and 'predicted' the bond-length of CO.

In this example, the molecule will end up with $r = r_0$, *i.e.* we have as an only answer the information introduced in the parameter list from experimental knowledge

(112.8 pm for CO). This will not be the case in more complicated molecules as you will see below. For CO, it is clear that the energy will become zero at r_0, *i.e.* the molecule is free of 'strain'. Again this will be different in more complicated cases.

Now let us see, how we could extend our mechanical model to also predict the structure of CO_2, which has longer bond-lengths (116.0 pm). We could assume that there is a repulsive force between atoms which are not directly bound. We could *e.g.* use the following assumption for this part of the potential:

$$E_r = c_2 e^{-r'}$$

r' is the distance between nonbonded atoms in our case between the two oxygens. c_2 is again an empirical parameter, which is stored in the program. Now the total energy for this molecule reads as:

$$E = 2 E_s + E_r = 2 c_1(r - r_0)^2 + c_2 e^{-r'}$$

Again the program can calculate E, having r and r' from the input data and it will find an energy minimum by systematically changing the distances. This time the final distance will be slightly longer due to the last term and the energy will not be exactly zero, which means that there will be some 'strain' in this molecule. 'Strain in CO_2' you might ask. Yes, but from the point of view of this force field, not in the usual chemical sense (the above force field is anyway not a very realistic one, but rather a simplified model designed to show the basic ideas). Such a simple example as this could easily be handled with paper and pencil, but medium sized molecules already need the help of a computer.

Now, what do we mean by a force field? The force field is generated from a set of assumptions using a necessary number of parameters. As you can imagine, the force field is the critical part of a molecular mechanics model. It depends on the force field how well experimental structures or enthalpies are modeled, and also how meaningful in the chemical sense, things like strain can be interpreted. Therefore, we will discuss in a later column aspects of force fields in more details.

Perhaps you are now eager to get experience on your personal computer. This would surely be the best way to get acquainted with molecular modeling. There are several good programs available which implement these two concepts, and you will find reviews about such programs in our column. Now, are you on your way?

Announcements

Workshop on Molecular Mechanics and Molecular Dynamics Simulations

Lausanne, October 2nd and 3rd, 1990

Organized by the Group of Swiss Computational Chemists (GSCC). Participants limited to 30. This workshop is intended to have a triple purpose: i) to present the basic features of the physical principles and mathematical formalism of these theoretical models; ii) to review their most important applications to chemistry and biology; iii) to enable the participants to have a first start in the practice of these techniques by performing some guided calculations. Lectures by H.J.C. Berendsen, Univ. of Groningen, M. Dobler, ETH Zürich, and S. Wodak, Free Univ. of Brussels. For further information contact: Prof. J. Weber, Dept. of Physical Chemistry, University of Geneva, 30, quai Ernest Ansermet, CH-1211 Geneva 4 (Tel.: 022/702 65 30; EM: WEBER@SC2A.UNIGE.CH; Fax: 022 29 61 02).

VIIth International Congress of Quantum Chemistry

Menton (France), July 2nd to 5th, 1991

Organized by the International Academy of Quantum Molecular Sciences.
List of Symposia: Dynamics & Photophysics; Molecular Magnets & Molecular Superconductors; Computers & New Algorithms; Organometallic & Bioinorganic Chemistry; Density Oriented Approaches; Organic Reaction Mechanisms; Methods in Theoretical Organic Chemistry; From Clusters to Molecular Solids. Plenary lectures by W.A. Goddard, R. Hoffmann, W. Kohn, W. Kutzelnigg, J.P. Malrieu, K.A. Müller, J.A. Pople, S. Shaik, K. Wiberg, and R.A. Wyatt. For further information contact: Prof. L. Salem, Lab. de Chimie Théorique, Bât. 490, Univ. de Paris Sud, F-91405 Orsay Cedex, France (Tel.: (33-1) 69 41 73 98; EM: SALEM@FRCTHO11.BITNET; Fax: (33-1) 69 41 61 72).

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ALCHEMY II: Molecular Modeling auf dem PC

Heinrich G. Bührer*

ALCHEMY II, Version 2.01
TRIPOS Associates, St. Louis, MO 63144, USA; Lieferant: Evans & Sutherland Computer GmbH, Stahlgruberring 32, D-8000 München 82
IBM-PC, XT, AT oder PS/2 oder kompatibler Computer mit mindestens 640 kB RAM, Harddisk, Maus, mathematischem Koprozessor und EGA-Bildschirm
Hewlett-Packard ColorPro Graphik-Plotter (sollen auch Kugel-Stäbchen-Modelle geplottet werden, ist eine Graphik-Erweiterung erforderlich)
Preis: US$ 450.- (für Schulen), sonst US$ 750.–, Mengenrabatte erhältlich
Zwei 3,5″-Disketten, ein Handbuch. Demodiskette erhältlich.
Apple Macintosh II, IIx oder IIcx mit mindestens 2 MB RAM. Preis: US$ 950.–, Mengenrabatte erhältlich.
Getestet wurde die IBM-Version auf einem IBM-PS/2 Modell 50.

Einleitung

ALCHEMY II gehört zur Gruppe der *Molecular Modeling Software*. Vom gleichen Hersteller stammt das modular aufgebaute Programm SYBYL, das auf Grossrechnern läuft. Demgegenüber ist ALCHEMY II eine einfachere, bereits auf einem Personal Computer lauffähige Software. Im Gegensatz zu älteren Programmen wie *Molecular Graphics on the IBM PC Microcomputer* (Academic Press) erlaubt es auch das direkte Zeichnen von Molekülen ohne Koordinateneingabe.

Programmaufbau

Die Installation des Programms auf der Harddisk ist problemlos. Das Hauptmenu ist wie folgt aufgebaut:

Im *Molekülfenster* werden Moleküle gezeichnet, Programmkonfigurationen durchgeführt und der Hilfstext wiedergegeben. Das *Menüfenster* umfasst u.a. die folgenden Funktionen:

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