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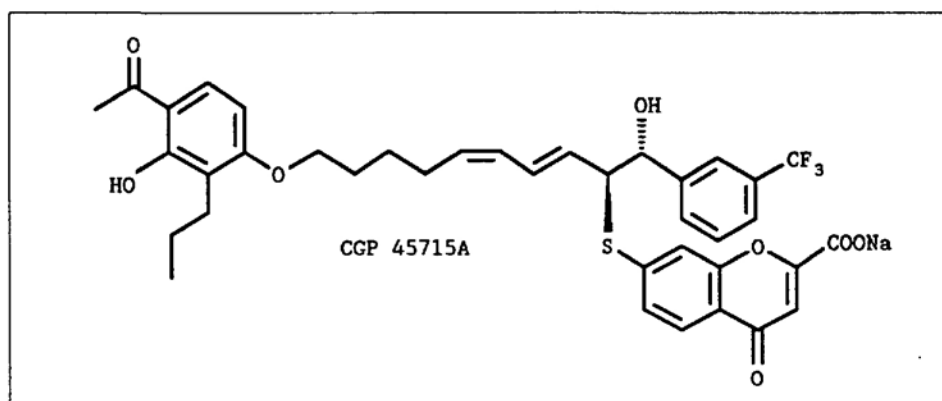
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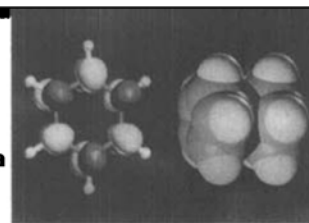
(Abstract by the authors)

CGP 45715A

COMPUTATIONAL CHEMISTRY COLUMN

Column Editors:
Prof. Dr. J. Weber, University of Geneva
PD Dr. H. Huber, University of Basel
Dr. H. P. Weber, Sandoz AG, Basel

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As the invited speaker *H. Berendsen* recently stated in Geneva, the future of molecular simulations lies undoubtedly in mixing more and more *Schrödinger* with *Newton*. In other words, realistic simulations of many-particle systems are going to be more and more performed by using *Newton*ian mechanics with interaction potentials parametrized in part by solving the *Schrödinger* equation. For quantum chemists proud of *Dirac* heritage ('the underlying physical laws...'), the pill could seem in a first sight somewhat bitter: why

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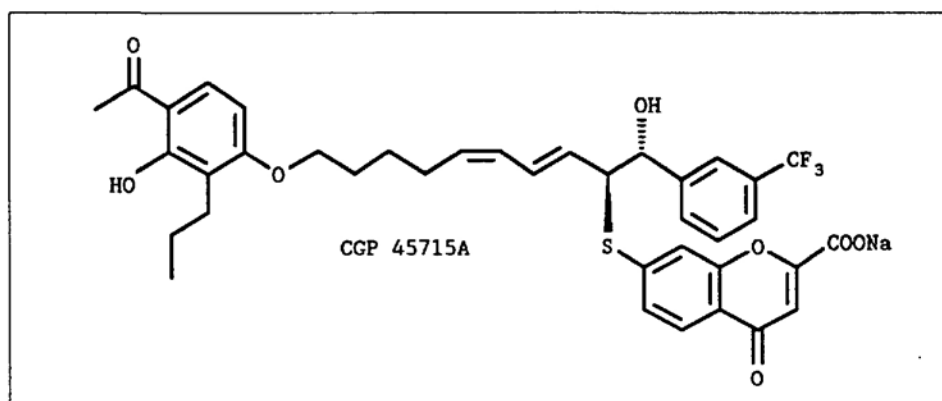
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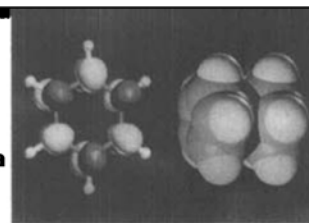
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band structures and nonlinear optical properties of these materials, as examples, which may lead to novel applications in semiconductors and electronic devices. However, for bulk properties of solids such as transport coefficients or heat capacity, quantum mechanical models are no longer adequate and have to be replaced by simulations allowing to describe the macroscopic behavior of these systems. The situation is the same for liquids, macro-molecules, and solutions, where numerical simulations of the dynamics of these collections of typically 10^2–10^5 atoms are essential to calculate their thermodynamic properties such as free energy and entropy or the folding topology of proteins.

The method of molecular dynamics (MD) is based on classical mechanics. It aims at modeling the interactions between particles in liquids and solids, and at solving the classical *Newton*'s equations of motion by numerical integration in order to evaluate the time evolution of the system. The first step is, therefore, to define an interaction potential $V(\vec{r}_1, ..., \vec{r}_N)$ between the N atoms of our system; the derivation of this potential function is a very delicate point, and we will come back to it further on. Let us just mention that, in the case of molecular crystals and liquids, the form of V is complicated by the fact that it should be able to describe both intra- and intermolecular interactions. The central idea of MD is then to solve the *Newton*'s 3N coupled differential equations:

$$\frac{d^2\vec{r}_i}{dt^2} = \frac{1}{m_i}\vec{F}_i$$

where the force $\vec{F}_i$ acting on atom i, with mass m_i and position $\vec{r}_i$, is defined by:

$$\vec{F}_i = -\vec{\nabla}_i \ V (\vec{r}_1,...,\vec{r}_N)$$

$\vec{\nabla}_i$ being the gradient operator corresponding to position $\vec{r}_i$.

The integration of *Newton*'s equations of motion for all particles of the system is performed numerically using small time steps of the order of 10^{-15} s, which leads to an estimation of their trajectories. Static equilibrium properties can then be extracted by averaging on the trajectories, provided the simulation is performed over a number of steps sufficient to lead to a representative ensemble of the state of the system, *i.e.* typically 10^4–10^5 steps. In many cases, an estimation of the dynamic properties of the system may also be obtained as the result of such modelizations. We shall come back more specifically on MD simulations in a further Column, and we would like to concentrate here on some basic aspects of such applications which require the use of quantum mechanics.

For a realistic simulation, the problem is now to have an accurate and computationally simple interaction potential $V(\vec{r}_1, ..., \vec{r}_N)$,

describing both long-range (*van der Waals* and *Coulombic*) and short-range (covalent) effects. As described in our previous Columns (July–August and November issues of *Chimia* 1990, *44*, 258, 377), $V(\vec{r}_1, ..., \vec{r}_N)$ is usually defined using empirical potential energy parameters, which leads to a so-called molecular force-field. One may find numerous force-fields in the literature, almost as many as there are computational chemists, and we would like to take a simple example of these formulations, which might write, for a system of N atoms, as

$$V = V_s + V_b + V_\chi + V_\phi + V_{nb}$$

where V_s, V_b, V_χ, V_ϕ, and V_{nb} represent bond-stretching, angle-bending, out-of-plane bending, torsional, and nonbonded interaction potentials, respectively; these expressions are usually written as

$$V_s = \frac{1}{2} \sum_{bonds} k_b \ (r-r_0)^2$$

$$V_b = \frac{1}{2} \sum_{\substack{bond \\ angles}} k_\vartheta \ (\vartheta-\vartheta_0)^2$$

$$V_\chi = \frac{1}{2} \sum_{\substack{out-of-plane \\ bends}} k_\chi \ (\chi-\chi_0)^2$$

where, in these harmonic potentials, $k_b, r_0, k_\vartheta, \vartheta_0, k_\chi$, and χ_0 are parameters characteristic of the force field;

$$V_\phi = \frac{1}{2} \sum_{\substack{dihedral \\ angles}} k_\phi \ (1+s \cos n_\phi)$$

is a torsional potential, the form and the values of k_ϕ, s, and n parameters of which being mostly dictated by the nature and periodicity of the torsional motion;

$$V_{nb} = \sum_{i,j} \left[c_{ij} \ r_{ij}^{-12} - d_{ij} \ r_{ij}^{-6} + \frac{q_{ij} q_{ij}}{4\pi\varepsilon \ r_{ij}} \right]$$

is a classical nonbonded potential composed of the 12–6 *van der Waals* and *Coulombic* (electrostatic) interactions, respectively.

Now, as you can imagine, setting up a consistent force-field, *i.e.* optimizing all the parameters of the potential energy function V to reproduce the structures of a coherent set of molecules, is a formidable task, complicated by the fact that the derivation of the force-field is not unique. In other words, there are several possible choices which lead to equally good results for the structural properties of a given molecule, and the problem is to obtain generalized force-fields with parameters transferable from system to system. Among the different strategies which have been suggested, the most successful parametrization procedure consists, according to *Allinger*, in 'optimizing the parameters by inspection or trial and error, *i.e.* minimizing the discrepancies with

structural data, and by using least-squares methods to supplement the error adjustments'. Actually, this procedure is a combination of two extreme strategies which have been used historically to set up the first force-fields:

i) an optimization of parameters 'by hand', *i.e.* by adjusting them in such a way as to minimize the errors with structural and energy data, and *ii*) the use of computerized least-squares methods optimizing the parameters in a statistical way. In cases where no experimental structural data exist, or for the determination of parameters such as the atomic charges q_i of the *Coulomb* potential, it is essential to perform *ab initio* quantum chemical calculations as an indispensable ingredient of the derivation of the force-field. This explains the provocative title of this Column: 'when *Schrödinger* and *Newton* work together...'

A first difficulty which arises when using quantum chemistry to derive a force-field lies in the fact that it would be useless to fit separately the various components of V, for example a parametrized V_{nb} against an *ab initio* one: the only point which makes sense is to have a total interaction potential V reproducing as closely as possible the main features of the *ab initio* potential energy surface, *i.e.* the position, energy depth, gradient, and curvature of the minima and of other points close to the minima as well, but also the transition states and characteristics far from the minima. This is essential for MD simulations where the trajectories of the atoms calculated by integration of the equations of motion may well lead to configurations typical of nonequilibrium situations.

The second problem associated with the use of *ab initio* techniques in force-field determination is concerned with the fuzzy definition of some quantities found in components of V, such as the atomic charges q_i. This is an important point, as the electrostatic interaction is a key factor to an accurate description of H-bonding and other long-range properties. It is, therefore, essential to derive a coherent set of atomic charges to be used in a force-field para-metrization, and two techniques have been mainly used to evaluate these quantities from *ab initio* or semiempirical wave functions: the *Mulliken* population analysis, which suffers from well-known drawbacks, and the fitting of molecular electrostatic potentials (MEP) by an approximate monopolar expansion, such as that recently proposed by *Kollman*. At first sight, one might think that the second procedure is superior, because it leads to a better description of electrostatic interactions between atoms and molecules. However, it requires the calculation of the MEP, which may be tedious for large molecules and fragments, and leads in practice to atomic charges 2–3 times larger, in absolute value, than those obtained through a *Mulliken* population analysis. This latter point

indicates that it is not possible to interchange different sets of atomic charges within existing force-fields and that the approach of the 'Force-field Consortium' (see this Column, November issue of *Chimia* **1990**, *44*, 377), consisting in the *de novo*

development of a completely new set of parameters, including atomic charges, is probably the best strategy towards a significant improvement of the performances of the models. Thanks to *Schrödinger*, the future of simulations based on *Newton*ian

mechanics is indeed very promising, but it will require patient and careful selections of potential functions and parameter optimizations before enlarging the range of present applications to complex macromolecules and new materials.

MoMo: a Molecular-Modelling Program

Georg Gescheidt*[a]) and Elisabeth Novotny-Bregger[b])

MoMo, Version 6.1
Author: *Max Dobler*, Laboratorium für Organische Chemie, ETH-Zentrum, CH–8092 Zürich
Distributor: The program is distributed by the author, Tel.: 01/256 45 09, Bitnet: DOBLER@CZHETH5A
Fee: SFr. 20.–
MoMo runs on all Macintosh computers *i.e.* MacPlus, Mac SE, SE/30, Macintosh II, IIcx, IIci, IIfx. It prints to any dot or laser printer. For unknown reasons, the program may cause problems on Macintoshes equipped with a non-apple monitor.
Program size: 122 kByte.
RAM required: *ca.* 300–400 kByte.
Installation: no installation procedure; start MoMo from Disk or copy to harddisk and start.

Chemists involved in various fields of activity are now more and more frequently using computers when studying molecular structures. Therefore, some of the major scientific software houses offer packages for this purpose. MoMo, a program developed for in-house use by Prof. *M. Dobler* at the ETH in Zürich, shows us what an easily learnable and usable chemist's tool can look like.

Program Description

When you start the program MoMo, a typical *Macintosh* window equipped with a menu bar and some buttons on the left- and right-hand side of the screen opens (*Fig.*). Now, you can read up to 400 atoms into each of the five available windows. *Cartesian* or crystal coordinates are required to read in the molecules or molecular assemblies. Furthermore, it is possible to add up to 20 symmetry operations leading to a representation of crystal lattices.

Correspondence: Dr. G. Gescheidt
ª) Institut für Physikalische Chemie
Universität Basel
Klingelbergstrasse 80
CH–4056 Basel
ᵇ) Laboratorium für organische Chemie
ETH-Zentrum
CH–8092 Zürich

After choosing a coordinate file of the adequate format, a model of the desired structure is displayed on the screen. By using the translation or rotation buttons of the MoMo window (see *Fig.*), the model is transformed step by step according to three orthogonal screen axes *x*, *y*, and *z*. After the selection of four atoms, the torsion angle is varied by pressing the 'torsion' button. The increments for the rotations and translations can be changed in four steps from 1 to 10° and 0.02 to 0.5 Å.

When you click two nonbonded atoms, their distance will be displayed along with a dotted line between them. After pressing the 'geom' button on the left-hand side of the screen, it changes to 'ok' and gives you access to bond lengths, bond angles, and torsion angles if two, three, and four consecutively bonded atoms, respectively, are 'clicked'.

The 400 atoms read into one MoMo window may come from up to four molecules. Each of these can be made active and singly manipulated as described above. Docking procedures can be performed with up to 10 nonbonded distances selected, the changing distances being displayed simultaneously.

In addition, MoMo includes features to modify imported structures: *i*) A new atom is attached by selecting the atom to which it is bound; two further atoms have to be chosen in order to define the bond and dihedral angles. *ii*) H-atoms can be added, and *iii*) bonds, or molecular fragments are deleted by a simple select-and-cut procedure. Furthermore, it is possible to fuse molecules, to superpose molecules, and to align a molecule along a given vector.

There are four different graphic representations available: *i*) a stick-type representation, *ii*) stick-type with bold bonds for atoms lying above the screen plane, *iii*) ball-and-stick, and *iv*) space-filling model. It is not possible to manipulate the models in the latter two drawing modes, *i.e.* they are static. In all drawing modes, the atom labels are highlighted as an option. A list of program features is summarized in the *Table*. MoMo does not include geometry-optimisation procedures.
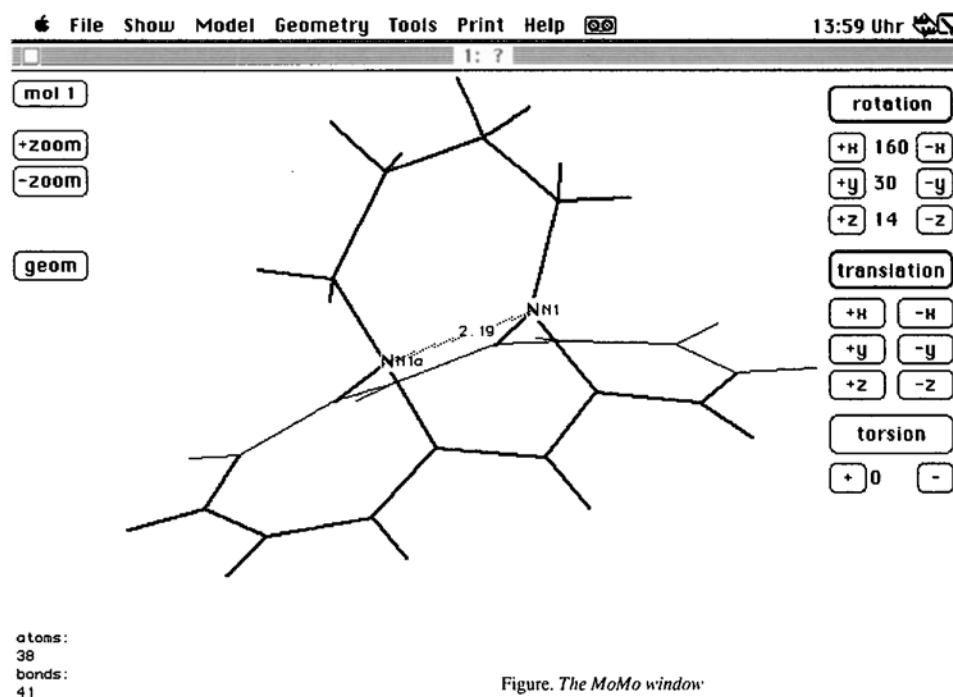

Figure. *The MoMo window*