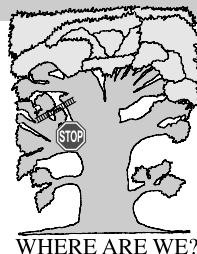# Chapter 7

# MOTION OF NUCLEI

## Where are we?

We are on the most important side branch of the TREE.

## An example

Which of conformations (Fig. 7.1) is more stable: the "boat" or "chair" of cyclohexane $C_6H_{12}$? How do particular conformations look in detail (symmetry, interatomic distances, bond angles), when the electronic energy as a function of the positions of the nuclei attains a minimum value? What will be the most stable conformation of the trimer: $C_6H_{11}$–$(CH_2)_3$–$C_6H_{10}$–$(CH_2)_3$–$C_6H_{11}$?
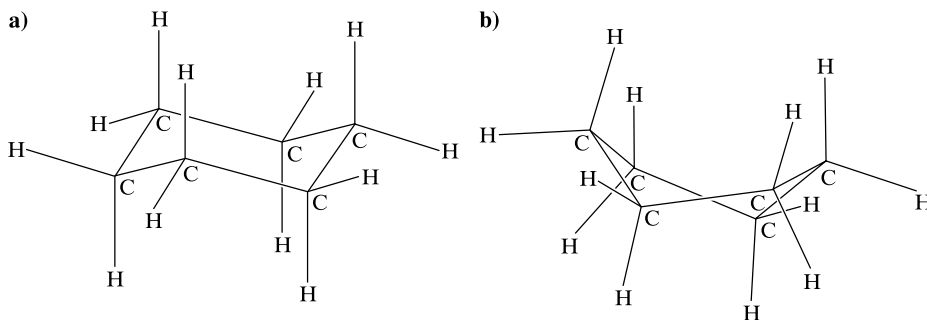
a)

b)



**Fig. 7.1.** The chair (a) and boat (b) conformations of cyclohexane. These geometries (obtained from arbitrary starting conformations) are optimized in the force field, which we will define in the present chapter. The force field indicates, in accordance with experimental results, that the chair conformation is the more stable (by about 5.9 kcal/mol). Thus we obtain all the details of the atomic positions (bond lengths, bond angles, etc.). Note that the chair conformation obtained exhibits $D_{3d}$ symmetry, while the boat conformation corresponds to $D_2$ (the boat has somewhat warped planks, because of repulsion of the two upper hydrogen atoms).

## What is it all about

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- Anisotropy of the potential $V$
- Adding the angular momenta in quantum mechanics
- Application of the Ritz method
- Calculation of rovibrational spectra

As shown in Chapter 6, the solution of the Schrödinger equation in the adiabatic approximation can be divided into two tasks: the problem of electronic motion in the field of the clamped nuclei (this will be the subject of the next chapters) and the problem of *nuclear motion in the potential energy determined by the electronic energy*. The ground-state electronic energy $E_k^0(\boldsymbol{R})$ of eq. (6.8) (where $k = 0$ means the ground state) will be denoted in short as $V(\boldsymbol{R})$, where $\boldsymbol{R}$ represents the vector of the nuclear positions. The function $V(\boldsymbol{R})$ has quite a complex structure and exhibits many basins of stable conformations (as well as many maxima and saddle points).

The problem of the shape of $V(\boldsymbol{R})$, as well as of the nuclear motion on the $V(\boldsymbol{R})$ hypersurface, will be the subject of the present chapter. It will be seen that the electronic energy can be computed within sufficient accuracy as a function of $\boldsymbol{R}$ only for very simple systems (such as an atom plus a diatomic molecule), for which quite a lot of detailed information can be obtained.

In practice, for large molecules, we are limited to only some approximations to $V(\boldsymbol{R})$ called *force fields*. After accepting such an approximation we encounter the problem of geometry optimization, i.e. of obtaining the most stable molecular conformation. Such a conformation is usually identified with a minimum on the electronic energy hypersurface, playing the role of the potential energy for the nuclei (*local molecular mechanics*). In practice we have the problem of the huge number of such minima. The real challenge in such

a case is finding the *most* stable structure, usually corresponding to the global minimum (*global molecular mechanics*) of $V(R)$.

Molecular mechanics does not deal with nuclear motion as a function of time as well as with the kinetic energy of the system. This is the subject of molecular dynamics, which means solving the Newton equation of motion for all the nuclei of the system interacting by potential energy $V(R)$. Various approaches to this question (of general importance) will be presented at the end of the chapter.

## Why is this important?

In 2001 the Human Genome Project, i.e. the sequencing of human DNA, was announced to be complete. This represents a milestone for humanity and its importance will grow steadily over the next decades. In the biotechnology laboratories DNA sequences will continue to be translated at a growing rate into a multitude of the protein sequences of amino acids. Only a tiny fraction of these proteins (0.1 percent?) may be expected to crystallize and then their atomic positions will be resolved by X-ray analysis. The *function* performed by a protein (e.g., an enzyme) is of crucial importance, rather than its sequence. The function depends on the 3D shape of the protein. For enzymes the cavity in the surface, where the catalytic reaction takes place is of great importance. The complex catalytic function of an enzyme consists of a series of elementary steps such as: molecular recognition of the enzyme cavity by a ligand, docking in the enzyme active centre within the cavity, carrying out a particular chemical reaction, freeing the products and finally returning to the initial state of the enzyme. The function is usually highly selective (pertains to a particular ligand only), precise (high yield reaction) and reproducible. To determine the function we must first of all identify the active centre and understand how it works. This, however, is possible either by expensive X-ray analysis of the crystal, or by a much less expensive theoretical prediction of the 3D structure of the enzyme molecule with atomic resolution accuracy. That is an important reason for theory development, isn't it?

It is not necessary to turn our attention to large molecules only. Small ones are equally important: we are interested in predicting their structure and their conformation.

## What is needed?

- Laplacian in spherical coordinates (Appendix H, p. 969, recommended).
- Angular momentum operator and spherical harmonics (Chapter 4, recommended).
- Harmonic oscillator (p. 166, necessary).
- Ritz method (Appendix L, p. 984, necessary).
- Matrix diagonalization (Appendix K, p. 982, necessary).
- Newton equation of motion (necessary).
- Chapter 8 (an exception: the Car–Parrinello method needs some results which will be given in Chapter 8, marginally important).
- Entropy, free energy, sum of states (necessary).

## Classical works

There is no more classical work on dynamics than the monumental "*Philosophiae Naturalis Principia Mathematica*", Cambridge University Press, A.D. 1687 of Isaac Newton. ★ The idea of the force field was first presented by Mordechai Bixon and Shneior Lifson in *Tetrahedron* 23 (1967) 769 and entitled "*Potential Functions and Conformations in Cycloalkanes*".

Isaac Newton (1643–1727), English physicist, astronomer and mathematician, professor at Cambridge University, from 1672 member of the Royal Society of London, from 1699 Director of the Royal Mint – said to be merciless to the forgers. In 1705 Newton became a Lord. In the *opus magnum* mentioned above he developed the notions of space, time, mass and force, gave three principles of dynamics, the law of gravity and showed that the later pertains to problems that differ enormously in their scale (e.g., the famous apple and the planets). Newton is also a founder of differential and integral calculus (independently from G.W. Leibnitz). In addition Newton made some fundamental discoveries in optics, among other things he is the first to think that light is composed of particles.

★ The paper by Berni Julian Alder and Thomas Everett Wainwright "*Phase Transition for a Hard Sphere System*" in *Journal of Chemical Physics*, 27 (1957) 1208 is treated as the beginning of the molecular dynamics. ★ The work by Aneesur Rahman "*Correlations in the Motion of Atoms in Liquid Argon*" published in *Physical Review*, A136 (1964) 405 for the first time used a realistic interatomic potential (for 864 atoms). ★ The molecular dynamics of a small protein was first described in the paper by Andy McCammon, Bruce Gelin and Martin Karplus under the title "*Dynamics of folded proteins*", *Nature*, 267 (1977) 585. ★ The simulated annealing method is believed to have been used first by Scott Kirkpatrick, Charles D. Gellat and Mario P. Vecchi in a work "*Optimization by Simulated Annealing*", *Science*, 220 (1983) 671. ★ The Metropolis criterion for the choice of the current configuration in the Monte Carlo method was given by Nicolas Constantine Metropolis, Arianna W. Rosenbluth, Marshal N. Rosenbluth, Augusta H. Teller and Edward Teller in the paper "*Equations of State Calculations by Fast Computing Machines*" in *Journal of Chemical Physics*, 21 (1953) 1087. ★ The Monte Carlo method was used first by Enrico Fermi, John R. Pasta and Stanisław Marcin Ulam during their stay in Los Alamos (E. Fermi, J.R. Pasta, S.M. Ulam, "*Studies of Non-Linear Problems*", vol. 1, *Los Alamos Reports*, LA-1940). Ulam and John von Neumann are the discoverers of cellular automata.

## 7.1  ROVIBRATIONAL SPECTRA – AN EXAMPLE OF ACCURATE CALCULATIONS: ATOM – DIATOMIC MOLECULE

One of the consequences of adiabatic approximation is the idea of the potential energy hypersurface $V(\boldsymbol{R})$ for the motion of nuclei. To obtain the wave function for the motion of nuclei (and then to construct the total product-like wave function for the motion of electrons and nuclei) we have to solve the Schrödinger equation with $V(\boldsymbol{R})$ as the potential energy. This is what this hypersurface is for. We will find rovibrational (i.e. involving rotations and vibrations) energy levels and the corresponding wave functions, which will allow us to obtain rovibrational spectra (frequencies and intensities) to compare with experimental results.

## 7.1.1 COORDINATE SYSTEM AND HAMILTONIAN

Let us consider a diatomic molecule AB plus a weakly interacting atom C (e.g., H–H ... Ar or CO ... He), the total system in its electronic ground state. Let us centre the origin of the body-fixed coordinate system[1] (with the axes oriented as in the space-fixed coordinate system, see Appendix I, p. 971) in the centre of mass of AB. The problem involves therefore $3 \times 3 - 3 = 6$ dimensions.

However strange it may sound, six is too much for contemporary (otherwise impressive) computer techniques. Let us subtract one dimension by assuming that no vibrations of AB occur (rigid rotator). The five-dimensional problem becomes manageable. The assumption about the stiffness of AB now also pays off because we exclude right away two possible chemical reactions C + AB → CA + B and C + AB → CB + A, and admit therefore only some limited set of nuclear configurations – only those that correspond to a weakly bound complex C + AB. This approximation is expected to work better when the AB molecule is

Carl Gustav Jacob Jacobi (1804–1851), German mathematical genius, son of a banker, graduated from school at the age of 12, then associated with the universities of Berlin and Königsberg. Jacobi made important contributions to number theory, elliptic functions, partial differential equations, analytical mechanics.

stiffer, i.e. has a larger force constant (and therefore vibration frequency).[2]

We will introduce the *Jacobi coordinates* (Fig. 7.2, cf. p. 776): three components of vector $\boldsymbol{R}$ pointing to C from the origin of the coordinate system (the length $R$

Jacobi coordinates



**Fig. 7.2.** The Jacobi coordinates for the C...AB system. The origin is in the centre of mass of AB (the distance AB is constant and equal to $r_{eq}$). The positions of atoms A and B are fixed by giving the angles $\theta$, $\phi$. The position of atom C is determined by three coordinates: $R$, $\Theta$ and $\Phi$. Altogether we have 5 coordinates: $R$, $\Theta$, $\Phi$, $\theta$, $\phi$ or $R$, $\hat{\boldsymbol{R}}$ and $\hat{\boldsymbol{r}}$.
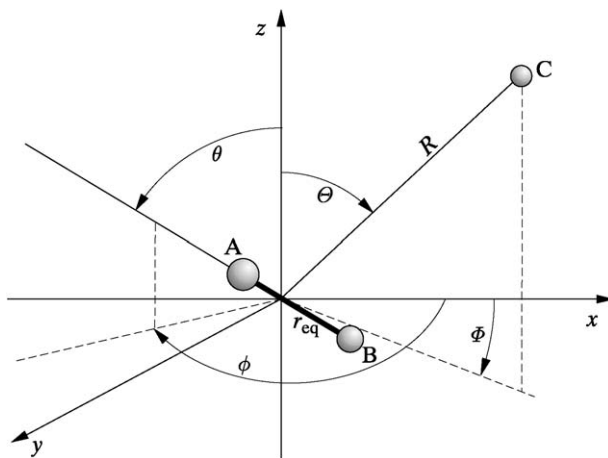
[1] Any coordinate system is equally good from the point of view of mathematics, but its particular choice may make the solution easy or difficult. In the case of a weak C ... AB interaction (our case) the proposed choice of the origin is one of the natural ones.

[2] A certain measure of this might be the ratio of the dissociation energy of AB to the dissociation energy of C...AB. The higher the ratio the better our model will be.

and angles $\Theta$ and $\Phi$, both angles denoted by $\hat{\boldsymbol{R}}$) and the angles $\theta$, $\phi$ showing the orientation $\hat{\boldsymbol{r}}$ of vector $\boldsymbol{r} = \overrightarrow{AB}$, altogether 5 coordinates – as there should be.

Now let us write down the Hamiltonian for the motion of the nuclei in the Jacobi coordinate system (with the stiff AB molecule with AB equilibrium distance equal to $r_{\text{eq}}$):[3]

$$\hat{H} = -\frac{\hbar^2}{2\mu R^2}\frac{\mathrm{d}}{\mathrm{d}R}R^2\frac{\mathrm{d}}{\mathrm{d}R} + \frac{\hat{l}^2}{2\mu R^2} + \frac{\hat{j}^2}{2\mu_{AB}r_{\text{eq}}^2} + V,$$

where $\hat{l}^2$ denotes the operator of the square of the angular momentum of the atom C, $\hat{j}^2$ stands for the square of the angular momentum of the molecule AB,

$$\hat{l}^2 = -\hbar^2\left[\frac{1}{\sin\Theta}\frac{\partial}{\partial\Theta}\sin\Theta\frac{\partial}{\partial\Theta} + \frac{1}{\sin^2\Theta}\frac{\partial^2}{\partial\Phi^2}\right],$$

$$\hat{j}^2 = -\hbar^2\left[\frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\sin\theta\frac{\partial}{\partial\theta} + \frac{1}{\sin^2\theta}\frac{\partial^2}{\partial\phi^2}\right],$$

$\mu$ is the reduced mass of C and the mass of (A + B), $\mu_{AB}$ denotes the reduced mass of A and B, $V$ stands for the potential energy of the nuclear motion.

The expression for $\hat{H}$ is quite understandable. First of all, we have in $\hat{H}$ five coordinates, as there should be: $R$, two angular coordinates hidden in the symbol $\hat{\boldsymbol{R}}$ and two angular coordinates symbolized by $\hat{\boldsymbol{r}}$ – the four angular coordinates enter the operators of the squares of the two angular momenta. The first three terms in $\hat{H}$ describe the kinetic energy, $V$ is the potential energy (the electronic ground state energy which depends on the nuclear coordinates). The kinetic energy operator describes the radial motion of C with respect to the origin (first term), the rotation of C about the origin (second term) and the rotation of AB about the origin (third term).

## 7.1.2 ANISOTROPY OF THE POTENTIAL $V$

How to figure out the shape of $V$? Let us first make a section of $V$. If we freeze the motion of AB,[4] the atom C would have (concerning the interaction energy) a sort of an energetic well around AB wrapping the AB molecule, caused by the C...AB van der Waals interaction, which will be discussed in Chapter 13. The bottom of the well would be quite distant from the molecule (van der Waals equilibrium distance), while the shape determined by the bottom points would resemble the shape of AB, i.e. would be a little bit elongated. The depth of the well would vary depending on orientation with respect to the origin.

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[3]The derivation of the Hamiltonian is given in S. Bratož, M.L. Martin, *J. Chem. Phys.* 42 (1965) 1051.
[4]That is, fixed the angles $\theta$ and $\phi$.

If $V$ were isotropic, i.e. if atom C would have C...AB interaction energy independent[5] of $\hat{\boldsymbol{r}}$, then of course we might say that there is no coupling between the rotation of C and the rotation of AB. We would have then a conservation law separately for the first and the second angular momentum and the corresponding commutation rules (cf. Chapter 2 and Appendix F)

$$[\hat{H}, \hat{l}^2] = [\hat{H}, \hat{j}^2] = 0,$$
$$[\hat{H}, \hat{l}_z] = [\hat{H}, \hat{j}_z] = 0.$$

Therefore, the wave function of the total system would be the eigenfunction of $\hat{l}^2$ and $\hat{l}_z$ as well as of $\hat{j}^2$ and $\hat{j}_z$. The corresponding quantum numbers $l = 0, 1, 2, \ldots$ and $j = 0, 1, 2, \ldots$ that determine the squares of the angular momenta $\boldsymbol{l}^2$ and $\boldsymbol{j}^2$, as well as the corresponding quantum numbers $m_l = -l, -l+1, \ldots, l$ and $m_j = -j, -j+1, \ldots, j$ that determine the projections of the corresponding angular momenta on the $z$ axis, would be legal[6] quantum numbers (full analogy with the rigid rotator, Chapter 4). The rovibrational levels could be labelled using pairs of quantum numbers: $(l, j)$. In the absence of an external field (no privileged orientation in space) any such level would be $(2l+1)(2j+1)$-tuply degenerate, since this is the number of different projections of both angular momenta on the $z$ axis.

### 7.1.3 ADDING THE ANGULAR MOMENTA IN QUANTUM MECHANICS

However, $V$ *is not isotropic* (although the anisotropy is small). What then? Of all angular momenta, only the *total* angular momentum $\boldsymbol{J} = \boldsymbol{l} + \boldsymbol{j}$ is conserved (the conservation law results from the very foundations of physics, cf. Chapter 2).[7] Therefore, the vectors $\boldsymbol{l}$ and $\boldsymbol{j}$ when added to $\boldsymbol{J}$, would make all allowed angles: from minimum angle (the quantum number $J = l + j$), through smaller angles[8] and the corresponding quantum numbers $J = l + j - 1, l + j - 2$, etc., up to the angle 180°, corresponding to $J = |l - j|$). Therefore, the number of all possible values of $J$ (each corresponding to a different energy) is equal to the number of projections of the *shorter*[9] of the vectors $\boldsymbol{l}$ and $\boldsymbol{j}$ on the longer one, i.e.

$$J = (l+j), (l+j-1), \ldots, |l-j|. \tag{7.1}$$

For a given $J$ there are $2J + 1$ projections of $\boldsymbol{J}$ on the $z$ axis (because $|M_J| \leqslant J$); without any external field all these projections correspond to identical energy.

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[5]I.e. the bottom of the well would be a sphere centred in the centre of mass of AB and the well depth would be independent of the orientation.

[6]We use to say "*good*".

[7]Of course, the momentum has also been conserved in the isotropic case, but in this case the energy was independent of the quantum number $J$ (resulting from different angles between $\boldsymbol{l}$ and $\boldsymbol{j}$).

[8]The projections of the angular momenta are quantized.

[9]In the case of two vectors of the same length, the role of the shorter vector may be taken by either of them.

Please check that the number of all possible eigenstates is equal to $(2l+1)(2j+1)$, i.e. exactly what we had in the isotropic case. For example, for $l=1$ and $j=1$ the degeneracy in the isotropic case is equal to $(2l+1)(2j+1) = 9$, while for anisotropic $V$ we would deal with 5 states for $J = 2$ (all of the same energy), 3 states corresponding to $J = 1$ (the same energy, but different from $J = 2$), a single state with $J = 0$ (still another value of energy), altogether 9 states. This means that switching anisotropy on partially removed the degeneracy of the isotropic level $(l, j)$ and gave the levels characterized by quantum number $J$.

### 7.1.4 APPLICATION OF THE RITZ METHOD

We will use the Ritz variational method (see Chapter 5, p. 202) to solve the Schrödinger equation. What should we propose as the expansion functions? It is usually recommended that we proceed systematically and choose first a complete set of functions depending on $R$, then a complete set depending on $\hat{R}$ and finally a complete set that depends on the $\hat{r}$ variables. Next, one may create the complete set depending on all five variables (these functions will be used in the Ritz variational procedure) by taking all possible products of the three functions depending on $R$, $\hat{R}$ and $\hat{r}$. There is no problem with the complete sets that have to depend on $\hat{R}$ and $\hat{r}$, as these may serve the spherical harmonics (the wave functions for the rigid rotator, p. 176) $\{Y_l^m(\Theta, \Phi)\}$ and $\{Y_{l'}^{m'}(\theta, \phi)\}$, while for the variable $R$ we may propose the set of harmonic oscillator wave functions $\{\chi_v(R)\}$.[10] Therefore, we may use as the variational function:[11]

$$\Psi(R, \Theta, \Phi, \theta, \phi) = \sum c_{vlml'm'} \chi_v(R) Y_l^m(\Theta, \Phi) Y_{l'}^{m'}(\theta, \phi),$$

where $c$ are the variational coefficients and the summation goes over $v, l, m, l', m'$ indices. The summation limits have to be finite in practical applications, therefore the summations go to some maximum values of $v$, $l$ and $l'$ ($m$ and $m'$ vary from $-l$ to $l$ and from $-l'$ to $+l'$). We hope (as always in quantum chemistry) that numerical results of a demanded accuracy will not depend on these limits. Then, as usual the Hamiltonian matrix is computed and diagonalized (see p. 982), and the eigenvalues $E_J$ as well as the eigenfunctions $\psi_{J,M_J}$ of the ground and excited states are found.

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[10]See p. 164. Of course, our system does not represent any harmonic oscillator, but what counts is that the harmonic oscillator wave functions form a complete set (as the eigenfunctions of a Hermitian operator).

[11]The products $Y_l^m(\Theta, \Phi)$ $Y_{l'}^{m'}(\theta, \phi)$ may be used to produce linear combinations that are automatically the eigenfunctions of $\hat{J}^2$ and $\hat{J}_z$, and have the proper parity (see Chapter 2). This may be achieved by using the Clebsch–Gordan coefficients (D.M. Brink, G.R. Satchler, "*Angular Momentum*", Clarendon, Oxford, 1975). The good news is that this way we can obtain a smaller matrix for diagonalization in the Ritz procedure, the bad news is that the matrix elements will contain more terms to be computed. The method above described will give the same result as using the Clebsch–Gordan coefficients, because the eigenfunctions of the Hamiltonian obtained within the Ritz method will automatically be the eigenfunctions of $\hat{J}^2$ and $\hat{J}_z$, as well as having the proper parity.

Each of the eigenfunctions will correspond to some $J$, $M_J$ and to a certain parity. The problem is solved.

## 7.1.5  CALCULATION OF ROVIBRATIONAL SPECTRA

The differences of the energy levels provide the electromagnetic wave *frequencies* needed to change the stationary states of the system, the corresponding wave functions enable us to compute the *intensities* of the rovibrational transitions (which occur at the far-infrared and microwave wavelengths). When calculating the intensities to compare with experiments we have to take into account the Boltzmann distribution in the occupation of energy levels. The corresponding expression for the intensity $I(J'' \to J')$ of the transition from level $J''$ to level $J'$ looks as follows:[12]

$$I\big(J'' \to J'\big) = (E_{J'} - E_{J''})\frac{\exp\big(\frac{E_{J''} - E_{J'}}{k_B T}\big)}{Z(T)} \sum_{m, M'_J, M''_J} \big|\langle \Psi_{J'M'_J}\big|\hat{\mu}_m\big|\Psi_{J''M''_J}\rangle\big|^2,$$

where:

- $Z(T)$ is the *partition function* (known from the statistical mechanics) – a function of the temperature $T$: $Z(T) = \sum_J (2J+1)\exp(-\frac{E_J}{k_B T})$, $k_B$ is the Boltzmann constant — partition function
- $\hat{\mu}_m$ represents the dipole moment operator (cf. Appendix X)[13] $\hat{\mu}_0 = \hat{\mu}_z$, $\hat{\mu}_1 = \frac{1}{\sqrt{2}}(\hat{\mu}_x + i\hat{\mu}_y)$, $\hat{\mu}_{-1} = \frac{1}{\sqrt{2}}(\hat{\mu}_x - i\hat{\mu}_y)$
- the rotational state $J''$ corresponds to the vibrational state 0, while the rotational state $J'$ pertains to the vibrational quantum number $v$, i.e. $E_{J''} \equiv E_{00J''}$, $E_{J'} \equiv E_{0vJ'}$ (index 0 denotes the electronic ground state)
- the integration is over the coordinates $R$, $\hat{\boldsymbol{R}}$ and $\hat{\boldsymbol{r}}$.

   The dipole moment in the above formula takes into account that the charge distribution in the C...AB system depends on the nuclear configuration, i.e. on $R$,

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[12]D.A. McQuarrie, "*Statistical Mechanics*", Harper&Row, New York, 1976, p. 471.

[13]The Cartesian components of the dipole moment operator read as

$$\hat{\mu}_x = \sum_{\alpha=1}^{M} Z_\alpha X_\alpha - \sum_{i=1}^{N} \langle \Psi_0^{el}\big|x_i\big|\Psi_0^{el}\rangle$$

and similarly for $y$ and $z$, where $Z_\alpha$ denotes the charge (in a.u.) of the nucleus $\alpha$, $X_\alpha$ denotes its $x$ coordinate,
- $\Psi_0^{el}$ denotes the electronic ground-state wave function of the system that depends parametrically on $R$, $\hat{\boldsymbol{R}}$ and $\hat{\boldsymbol{r}}$;
- $M = 3$, $N$ stands for the number of electrons in C... AB;
- $i$ is the electron index;
- the integration goes over the electronic coordinates.

Despite the fact that, for charged systems, the dipole moment operator $\hat{\boldsymbol{\mu}}$ depends on the choice of the origin of the coordinate system, the integral itself does not depend on such choice (good for us!). Why? Because these various choices differ by a constant vector (an example will be given in Chapter 13). The constant vector goes out of the integral and the corresponding contribution, depending on the choice of the coordinate system, gives 0, because of the orthogonality of the states.
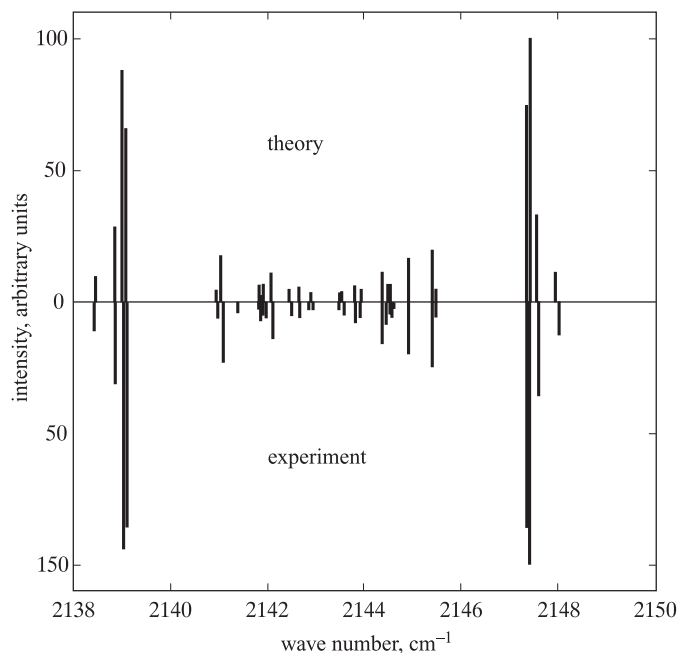
**Fig. 7.3.** Comparison of the theoretical and experimental intensities of the rovibrational transitions (in cm$^{-1}$) for the $^{12}$C$^{16}$O ... $^4$He complex. Courtesy of Professor R. Moszyński.

$\hat{R}$ and $\hat{r}$, e.g., the atom C may have a net charge and the AB molecule may change its dipole moment when rotating.

Heijmen et al. carried out accurate calculations of the hypersurface $V$ for a few atom-diatomic molecules, and then using the method described above the Schrödinger equation is solved for the nuclear motion. Fig. 7.3 gives a comparison of theory[14] and experiment[15] for the $^{12}$C$^{16}$O complex with the $^4$He atom.[16]

All the lines follow from the electric-dipole-allowed transitions [those for which the sum of the integrals in the formula $I(J'' \to J')$ is not equal to zero], each line is associated with a transition $(J'', l'', j'') \to (J', l', j')$.

## 7.2 FORCE FIELDS (FF)

The middle of the twentieth century marked the end of a long period of determining the building blocks of chemistry: chemical elements, chemical bonds, bond angles. The lists of these are not definitely closed, but future changes will be rather cosmetic than fundamental. This made it possible to go one step further and begin

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[14]T.G.A. Heijmen, R. Moszyński, P.E.S. Wormer, A. van der Avoird, *J. Chem. Phys.* 107 (1997) 9921.

[15]C.E. Chuaqui, R.J. Le Roy, A.R.W. McKellar, *J. Chem. Phys.* 101 (1994) 39; M.C. Chan, A.R.W. McKellar, *J. Chem. Phys.* 105 (1996) 7910.

[16]Of course the results depend on the isotopes involved, even when staying within the Born–Oppenheimer approximation.

to rationalize the structure of molecular systems as well as to foresee the structural features of the compounds to be synthesized. The crucial concept is based on the adiabatic (or Born–Oppenheimer) approximation and on the theory of chemical bonds and resulted in the spatial structure of molecules. The great power of such an approach was proved by the construction of the DNA double helix model by Watson and Crick. The first DNA model was build from iron spheres, wires and tubes. This approach created problems: one of the founders of force fields, Michael Levitt, recalls[17] that a model of a tRNA fragment constructed by him with 2000 atoms weighted more than 50 kg.

The experience accumulated paid off by proposing some approximate expressions for electronic energy, which is, as we know from Chapter 6, the potential energy of the motion of the nuclei. This is what we are going to talk about.

Suppose we have a molecule (a set of molecules can be treated in a similar way). We will introduce the *force field,* which will be a *scalar* field – a function $V(\boldsymbol{R})$ of the nuclear coordinates $\boldsymbol{R}$. The function $V(\boldsymbol{R})$ represents a generalization (from one dimension to $3N-6$ dimensions) of the function $E_0^0(R)$ of eq. (6.8) on p. 225. The force acting on atom $j$ occupying position $x_j, y_j, z_j$ is computed as the components of the vector $\boldsymbol{F}_j = -\nabla_j V$, where

James Dewey Watson, born 1928, American biologist, professor at Harvard University. Francis Harry Compton Crick (1916–2004), British physicist, professor at Salk Institute in San Diego. Both scholars won the 1962 Nobel Prize for "*their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material*". At the end of the historic paper J.D. Watson, F.H.C. Crick, *Nature*, 737 (1953) (of about 800 words) the famous enigmatic but crucial sentence appears: "*It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material*". The story behind the discovery is described in a colourful and unconventional way by Watson in his book "*Double Helix: A Personal Account of the Discovery of the Structure of DNA*".

$$\nabla_j = \boldsymbol{i} \cdot \frac{\partial}{\partial x_j} + \boldsymbol{j} \cdot \frac{\partial}{\partial y_j} + \boldsymbol{k} \cdot \frac{\partial}{\partial z_j} \qquad (7.2)$$

with $\boldsymbol{i}, \boldsymbol{j}, \boldsymbol{k}$ denoting the unit vectors along $x, y, z$, respectively.

> **FORCE FIELD**
> A force field represents a mathematical expression $V(\boldsymbol{R})$ for the electronic energy as a function of the nuclear configuration $\boldsymbol{R}$.

Of course, if we had to write down this scalar field in a 100% honest way, we have to solve (with an accuracy of about 1 kcal/mol) the electronic Schrödinger

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[17] M. Levitt, *Nature Struct. Biol.* 8 (2001) 392.

equation (6.8) for every configuration $\boldsymbol{R}$ of the nuclei and take the eigenvalue [i.e. an analogue of $E_0^0(R)$] as $V(\boldsymbol{R})$. This would take so much time, even for small systems composed of a few atoms, that maybe even after some cursing, we would abandon this method with a great feeling of relief. Even if such a calculation required huge computation time, it would give results which would have been quite simple in their overall features (assuming that the molecule has a pattern of chemical bonds). It just would turn out that $V$ would be characterized by the following:

- **Chemical bonds.** $V(\boldsymbol{R})$ would be obtained about its minimum, if any chemical bond between atoms $X$ and $Y$ had *a certain characteristic reference length* $r_0$ that would depend on the chemical species of the atoms $X$ and $Y$. If the bond length were changed (shortened or elongated) to a certain value $r$, the energy would increase, first according to the harmonic law (with force constant $k_{XY}$) and then some deviations from the harmonic approximation begin.[18] A harmonic term of the kind $\frac{1}{2}k_{XY}(r-r_0)^2$ incorporated additively into $V$ replaces the true anharmonic dependence by a harmonic approximation (assumption of small amplitudes) as if the two atoms had been bound by a harmonic spring (in the formula the atomic indices at symbols of distances have been omitted). The most important feature is that the same formula $\frac{1}{2}k_{XY}(r-r_0)^2$ is used for all chemical bonds $X$–$Y$, *independently of some particular chemical neighbourhood of a given $X$–$Y$ bond*. For example, one assumes that a non-distorted single C–C bond[19] has a characteristic reference length $r_0 = 1.523$ Å and a characteristic force constant $k_{XY} = 317 \frac{\text{kcal}}{\text{mol Å}^2}$, similarly, some distinct parameters pertain to the C=C bond: $r_0 = 1.337$ Å, $k_{XY} = 690 \frac{\text{kcal}}{\text{mol Å}^2}$ etc.[20, 21]

- **Bond angles.** While preserving the distances $r$ in the A–B and B–C bonds we may change the bond angle $\alpha =$ A–B–C, in this way changing the A...C distance. A corresponding change of $V$ has to be associated with such a change. The energy has to increase when the angle $\alpha$ deviates from a characteristic reference value $\alpha_0$. The harmonic part of such a change may be modelled by $\frac{1}{2}k_{XYZ}(\alpha - \alpha_0)^2$ (the indices for angles are omitted), which is equivalent to setting a corresponding harmonic spring for the bond angle and requires small amplitudes $|\alpha - \alpha_0|$. For example, for the angle C–C–C $\alpha_0 = 109.47°$ and $k_{XYZ} = 0.0099 \frac{\text{kcal}}{\text{mol degree}^2}$, which means that to change the C...C distance by varying angle is about an order of magnitude easier than to change a CC bond length.

---

[18]These deviations from harmonicity (i.e. from the proportionality of force and displacement) are related to the smaller and smaller force needed to elongate the bond by a unit length and the larger and larger force needed to shorten the bond.

[19]That is, when all other terms in the force field equal zero.

[20]A CC bond involved in a conjugated single and double bonds (e.g., in benzene) also has its own parameters.

[21]A description of the popular MM2 force field is given in N.L. Allinger, *J. Am. Chem. Soc.* 99 (1977) 8127.

- **van der Waals interaction.** Two atoms X and Y, that do not form a chemical bond X–Y, as well as not participating in any sequence of bonds X–A–Y, still interact. There is nothing in the formulae introduced above that would prevent X and Y *collapsing* without any change of $V$. However, when two such atoms approach at a distance smaller than the sum of their radii (the van der Waals radii, see p. 742), then $V$ had to increase very greatly.[22] On the other hand, at large interatomic distances the two atoms have to attract each other by the dispersion interaction vanishing as $r^{-6}$ (cf. Chapter 13, p. 694). Hence, there is an

John E. Lennard-Jones was professor of theoretical chemistry of the University of Cambridge, UK. The reader may find a historic picture of the theoretical chemistry team in *Intern. J. Quantum Chemistry*, S23 (1989), page XXXII.

equilibrium distance $r_e$, at which the interaction energy attains a minimum equal to $-\varepsilon$. These features of the interaction are captured by the widely used Lennard-Jones potential

$$V_{LJ}(X,Y) = \varepsilon\left[\left(\frac{r_e}{r}\right)^{12} - 2\left(\frac{r_e}{r}\right)^{6}\right],$$

where we skip for brevity the indices $X, Y$ on the right-hand side. The Lennard-Jones potential given above is called LJ 12–6 (reflecting the powers involved). Sometimes other powers are used leading to other "LJ m–n" potentials.[23] Due to their simplicity, the LJ potentials are widely used, Fig. 7.4.

Lennard-Jones potential

**Fig. 7.4.** The Lennard-Jones (LJ 12–6) potential. The parameter $\varepsilon > 0$ represents the depth of the potential well, while the parameter $r_e$ denotes the minimum position. This $r_e$, corresponding to the *nonbonding* interaction of atoms X and Y, has no direct relation to the $r_0$ value pertaining to the chemical bond X–Y (discussed above; in order to keep the notation concise we do not distinguish between the two). The first is larger than the second by about an angstrom or so.



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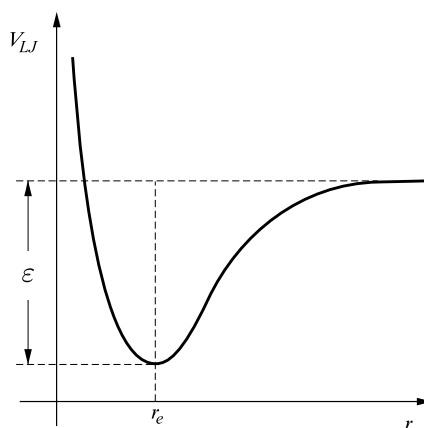
[22]A similar thing happens with cars: the repair cost increases very greatly, when the distance between two cars decreases below two thicknesses of the paint job.

[23]The power 12 has been chosen for two reasons: first, the power is sufficiently large to produce a strong repulsion when the two atoms approach each other, second, ... $12 = 6 \times 2$. The last reason makes the first derivative formula (i.e. the force) look more elegant than other powers do. A more elegant formula is often faster to compute and this is of practical importance.

- **Electrostatic interaction.** All the terms we have introduced to $V$ so far do not take into account the fact that atoms carry net charges $q_X$ and $q_Y$ that have to interact electrostatically by Coulombic forces. To take this effect into account the electrostatic energy terms $q_X q_Y / r$ are added to $V$, where we assume the net charges $q_X$ and $q_Y$ are fixed (i.e. independent of the molecular conformation).[24]

- **Torsional interactions.** In addition to all the terms described above we often introduce to the force field a torsional term $A_{X-Y-Z-W}(1 - \cos n\omega)$ for each torsional angle $\omega$ showing how $V$ changes when a rotation $\omega$ about the chemical bond YZ, in the sequence X–Y–Z–W of chemical bonds, takes place ($n$ is the multiplicity of the energy barriers per single turn[25]). Some rotational barriers already result from the van der Waals interaction of the X and W atoms, but in practice the barrier heights have to be corrected by the torsional potentials to reproduce experimental values.

- **Mixed terms.** Besides the above described terms one often introduces some *coupling (mixed) terms*, e.g., bond–bond angle etc. The reasoning behind this is simple. The bond angle force constant X–Y–Z has to depend on the bond-lengths X–Y and Y–Z, etc.

Summing up a simple force field might be expressed as shown in Fig. 7.5, where for the sake of simplicity the indices $X$, $Y$ at $r$, $r_0$, as well as $X$, $Y$, $Z$ at $\alpha$, $\alpha_0$, and $X$, $Y$, $Z$, $W$ at $\omega$ have been omitted:

$$
V = \sum_{X-Y} \frac{1}{2} k_{XY}(r - r_0)^2 + \sum_{X-Y-Z} \frac{1}{2} k_{XYZ}(\alpha - \alpha_0)^2 + \sum_{X...Y} V_{LJ}(X, Y)
$$

$$
+ \sum_{X,Y} \frac{q_X q_Y}{r} + \sum_{\text{tors}} A_{X-Y-Z-W}(1 - \cos n\omega) + \text{coupling terms (if any)}.
$$

Such simple formulae help us to figure out how the electronic energy looks as a function of the configuration of the nuclei. Our motivation is as follows:

- economy of computation: *ab initio* calculations of the electronic energy for larger molecules would have been many orders of magnitude more expensive;

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[24]In some force fields the electrostatic forces depend on the dielectric constant of the neighbourhood (e.g., solvent) despite the fact that this quantity has a macroscopic character and does not pertain to the nearest neighbourhood of the interacting atoms. If all the calculations had been carried out taking the molecular structure of the solvent into account as well as the polarization effects, no dielectric constant would have been needed. If this is not possible, then the dielectric constant effectively takes into account the polarization of the medium (including reorientation of the solvent molecules). The next problem is *how* to introduce the dependence of the electrostatic interaction of two atomic charges on the dielectric constant. In some of the force fields we introduce a brute force kind of damping, namely, the dielectric constant is introduced into the denominator of the Coulombic interaction as equal to the ... interatomic distance.

In second generation force fields (e.g., W.D. Cornell, P. Cieplak, C.I. Bayly, I.R. Gould, K.M. Merz Jr., D.M. Ferguson, D.C. Spellmeyer, T. Fox, J.W. Caldwell, P.A. Kollman, *J. Amer. Chem. Soc.* 117 (1995) 5179) we explicitly take into account the induction interaction, e.g., the dependence of the atomic electric charges on molecular conformations.
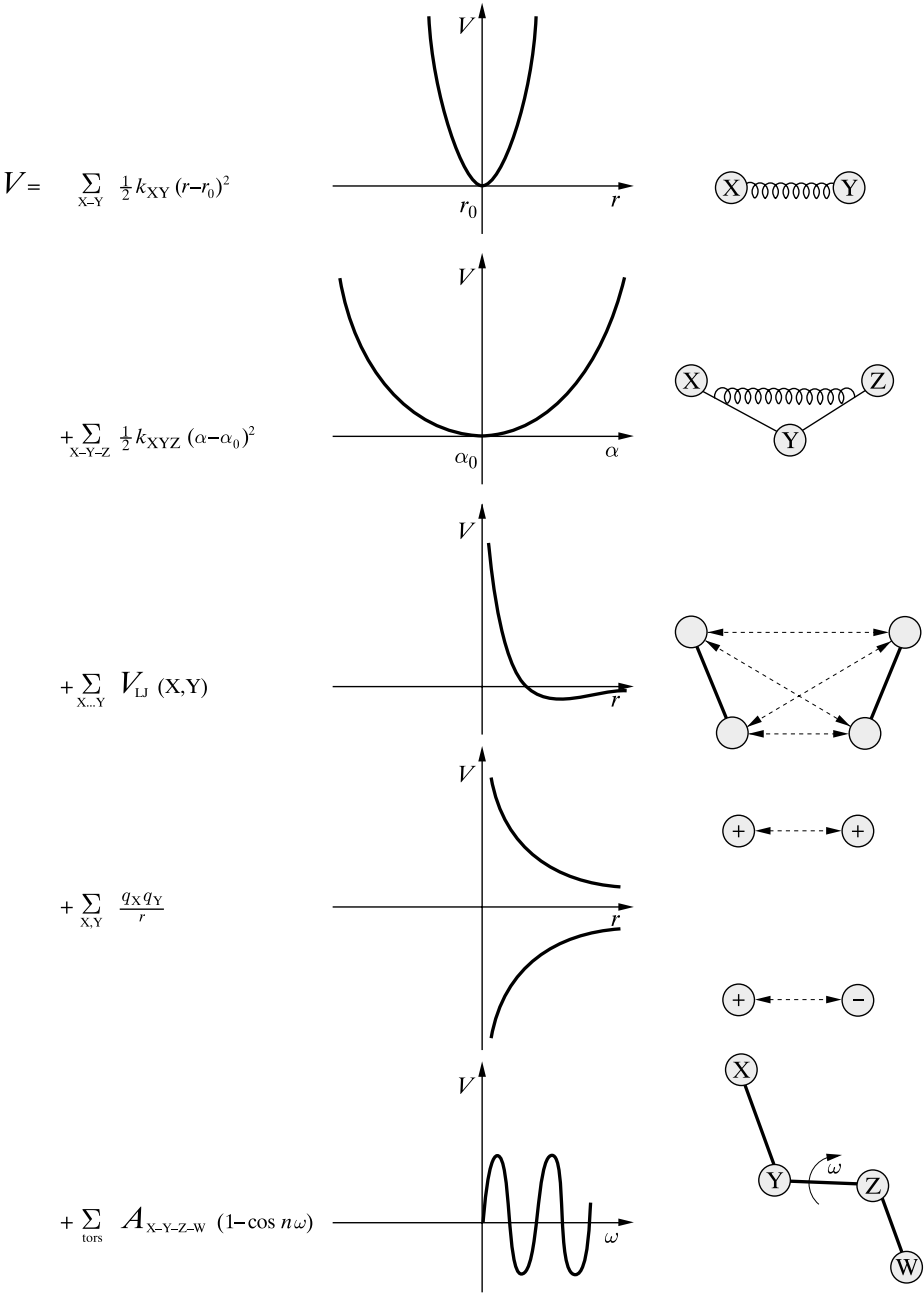
[25]For example, $n = 3$ for ethane.

$$V = \sum_{\text{X–Y}} \tfrac{1}{2} k_{\text{XY}} (r - r_0)^2$$

$$+ \sum_{\text{X–Y–Z}} \tfrac{1}{2} k_{\text{XYZ}} (\alpha - \alpha_0)^2$$

$$+ \sum_{\text{X...Y}} V_{\text{LJ}} (\text{X,Y})$$

$$+ \sum_{\text{X,Y}} \frac{q_{\text{X}} q_{\text{Y}}}{r}$$

$$+ \sum_{\text{tors}} A_{\text{X–Y–Z–W}} (1 - \cos n\omega)$$

**Fig. 7.5.** The first force field of Bixon and Lifson in a mnemonic presentation.

- in addition, a force field gives $V(\boldsymbol{R})$ in the form of a simple formula for *any* positions $\boldsymbol{R}$ of the nuclei, while the calculation of the electronic energy would give us $V(\boldsymbol{R})$ numerically, i.e. for some *selected* nuclear configurations.

## 7.3 LOCAL MOLECULAR MECHANICS (MM)

### 7.3.1 BONDS THAT CANNOT BREAK

It is worth noting that the force fields correspond to a fixed (and unchangeable during computation) system of chemical bonds. The chemical bonds are treated as springs, most often satisfying Hooke's[26] law (harmonic), and therefore unbreakable.[27] Similarly, the bond angles are forced to satisfy Hooke's law. Such a force field is known as *flexible molecular mechanics*. To decrease the number of variables, we sometimes use *rigid molecular mechanics*,[28] in which the bond lengths and the bond angles are fixed at values close to experimental ones, but the torsional angles are free to change. The argument behind such a choice is that the frequencies associated with torsional motion are much lower than those corresponding to the bond angle changes, and much much lower than frequencies of the bond length vibrations. This means that a quantity of energy is able to make only tiny changes in the bond lengths, small changes in the bond angles and large changes in the torsional angles, i.e. the torsional variables determine the overall changes of the molecular geometry. Of course, the second argument is that a smaller number of variables means lower computational costs.

flexible MM

rigid MM

> Molecular mechanics represents a method of finding a stable configuration of the nuclei by using a minimization of $V(\boldsymbol{R})$ with respect to the nuclear coordinates (for a molecule or a system of molecules).

The essence of molecular mechanics is that we roll the potential energy hypersurface slowly downhill from a starting point chosen (corresponding to a certain starting geometry of the molecule) to the "nearest" energy minimum corresponding to the final geometry of the molecule. The "rolling down" is carried out by a minimization procedure that traces point by point the trajectory in the configurational space, e.g., in the direction of the negative gradient vector calculated at any consecutive point. The minimization procedure represents a mechanism showing how to obtain the next geometry from the previous one. The procedure ends,

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[26]Robert Hooke, British physicist and biologist (1635–1703).

[27]There are a few such force fields in the literature. They give similar results, as far as their main features are considered. The force field concept was able to clarify many observed phenomena, even fine effects. It may also fail as with anything confronting the real world.

[28]Stiff molecular mechanics was a very useful tool for Paul John Flory (1910–1985), American chemist, professor at the universities at Cornell and Stanford. Using such mechanics, Flory developed a theory of polymers that explained their physical properties. In 1974 he obtained the Nobel Prize "*for his fundamental achievements, both theoretical and experimental, in the physical chemistry of macromolecules*".

when the geometry ceases to change (e.g., the gradient vector has zero length[29]). The geometry attained is called the equilibrium or stable geometry. The rolling described above is more like a crawling down with large friction, since in molecular mechanics the kinetic energy is always zero and the *system is unable to go uphill*[30] of $V$.

A lot of commercial software[31] offers force field packets. For example, the Hyperchem package provides the force fields AMBER and MM2,[32] the program Insight offers the CVFF force field. Unfortunately, the results depend to quite a significant degree on the force field chosen. Even using the same starting geometry we may obtain final (equilibrium) results that differ very much one from another. Usually the equilibrium geometries obtained in one force field do not differ much from those from another one, but the corresponding energies may be very different. Therefore, the most stable geometry (corresponding to the lowest energy) obtained in a force field may turn out to be less stable in another one, thus leading to different predictions of the molecular structure.

A big problem in molecular mechanics is that the final geometry is very close to the starting one. We start from a boat (chair) conformation of cyclohexane and obtain a boat (chair) equilibrium geometry. The very essence of molecular mechanics however, is that when started from some, i.e. distorted boat (chair) conformation, we obtain the perfect, beautiful equilibrium boat (chair) conformation, which may be compared with experimental results. Molecular mechanics is extremely useful in conformational studies of systems with a small number of stable conformations, either because the molecule is small, rigid or its overall geometry is fixed. In such cases all or all "reasonable",[33] conformations can be investigated and those of lowest-energy can be compared with experimental results.

## 7.3.2 BONDS THAT CAN BREAK

Harmonic bonds cannot be broken and therefore molecular mechanics with harmonic approximation is unable to describe chemical reactions. When instead of harmonic oscillators we use Morse model (p. 169), then the bonds can be broken.

And yet we most often use the harmonic oscillator approximation. Why? There are a few reasons:

- the Morse model requires many computations of the exponential function, which is expensive[34] when compared to the harmonic potential;

---

[29]The gradient is also equal zero at energy maxima and energy saddle points. To be sure that a minimum really has been finally attained we have to calculate (at the particular point suspected to be a minimum) a Hessian, i.e. the matrix of second derivatives of $V$, then diagonalize it (cf. p. 982) and check whether the eigenvalues obtained are all positive.

[30]Unless assuming too large a step (but this has to be considered as an error in the "art of computing").

[31]See the Web Annex.

[32]N.L. Allinger, *J. Am. Chem. Soc.* 99 (1977) 8127.

[33]A very dangerous word!

[34]Each time requires a Taylor expansion calculation.

- the Morse potential requires three parameters, while the harmonic model needs only two parameters;
- in most applications the bonds do not break and it would be very inconvenient to obtain breaking due, for instance, to a particular starting point;
- a description of chemical reactions requires not only the possibility of breaking bonds, but also a realistic, i.e. quantum chemical, computation of the charge distributions involved (cf. p. 308). The Morse potential would be too simplistic for such purposes.

## 7.4  GLOBAL MOLECULAR MECHANICS

### 7.4.1  MULTIPLE MINIMA CATASTROPHE

If the number of local minima is very large (and this may happen even for medium size molecules) or even "astronomic", then exploring the whole conformational space (all possible geometries) by finding all possible minima using a minimization procedure becomes impossible. Hence, we may postulate another procedure which may be called *global molecular mechanics* and could find the global minimum (the most stable conformation) starting from any point in the configurational space.

If the number of local minima is small, there is in principle no problem with using theory. Usually it turns out that the quantum mechanical calculations are feasible, often even at the *ab initio* level. A closer insight leads, however, to the conclusion that only some extremely accurate and expensive calculations would give the correct energy sequence of the conformers, and that only for quite small molecules with a dozen atoms. This means that for larger molecules we are forced to use molecular mechanics. For molecules with a few atoms we might investigate the whole conformational space by sampling it by a stochastic or systematic procedure, but this approach soon becomes prohibitive for larger molecules.

For such larger molecules we encounter difficulties which may only be appreciated by individuals who have made such computations themselves. We may say, in short, that virtually nothing helps us with the huge number of conformations to investigate. According to Schepens[35] the number of the conformations found is proportional to the time spent conducting the search. It is worth noting that this means catastrophe, because for a twenty amino acid oligopeptide the number of conformations is of the order[36] of $10^{20}$, and for a hundred amino acids –

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[35]Wijnand Schepens, PhD thesis, University of Gand, 2000.

[36]The difficulty of finding a particular conformation among $10^{20}$ conformations is a real horror. Maybe the example below will show what a severe problem has been encountered. A single grain of sand has a diameter of about 1 mm. Let us try to align $10^{20}$ of such sand grains side by side. What will the length of such a chain of grains be? Let us compute: $10^{20}$ mm $= 10^{17}$ m $= 10^{14}$ km. One light year is $300000$ km/s $\times 3600$ s $\times 24 \times 365 \simeq 10^{13}$ km. Hence, the length is about 10 light years, i.e. longer than the round trip from our Sun to the nearest star – Alpha Centauri. This is what the thing looks like.

$10^{100}$. Also methods based on molecular dynamics (cf. p. 304) do not solve the problem, since they could cover only a tiny fraction of the total conformational space.

## 7.4.2 IS IT THE GLOBAL MINIMUM WHICH COUNTS?

The goal of conformational analysis is to find those conformations of the molecule which are observed under experimental conditions. At temperatures close to 300 K the lowest-energy conformations prevail in the sample, i.e. first of all those corresponding the global minimum of the potential energy[37] $V$.

We may ask whether indeed the global minimum of the potential energy decides the observed experimental geometry. Let us neglect the influence of the solvent (neighbourhood). A better criterion would be the global minimum of the *free energy*, $E - TS$, where the entropic factor would also enter. A wide potential well means a higher density of vibrational states, a narrow well means a lower density of states (cf. eq. (4.21), p. 171; a narrow well corresponds to a large $\alpha$). If the global minimum corresponds to a wide well, the well is additionally stabilized by the entropy,[38] otherwise it is destabilized.

<div style="float:right">free energy</div>

For large molecules, there is a possibility that, due to the synthesis conditions, the molecule is trapped in a local minimum (*kinetic minimum*), different from the global minimum of the free energy (*thermodynamic minimum*), Fig. 7.6.

<div style="float:right">kinetic minimum</div>

For the same reason that the diamonds (kinetic minimum) in your safe do not change spontaneously into graphite (thermodynamic minimum), a molecule imprisoned in the kinetic minimum may rest there for a very long time (when compared with experimental time). Nobody knows whether the native conformation of

<div style="float:right">thermodynamic minimum</div>



**Fig. 7.6.** Electronic energy $V(\boldsymbol{R})$ as function of the nuclear configuration $\boldsymbol{R}$. The basins of the *thermodynamic minimum* (T), of the *kinetic minimum* (K) and of the *global* minimum (G). The deepest basin (G) should not correspond to the thermodynamically most stable conformation (T). Additionally, the system may be caught in a kinetic minimum (K), from which it may be difficult to tunnel to the thermodynamic minimum basin. Diamond and fullerenes may serve as examples of K.

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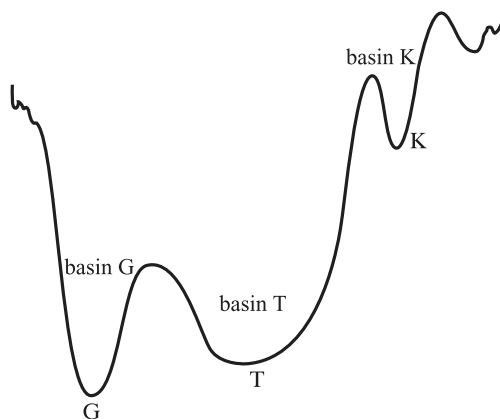
[37]Searching for the global minimum of $V$ is similar to the task of searching for the lowest valley on Earth when starting from an arbitrary point on the surface.

[38]According the famous formula of Ludwig Boltzmann, entropy $S = k_B \ln \Omega(E)$, where $\Omega$ is the number of the states available for the system at energy $E$. The more states, the larger the entropy.

Christian Anfinsen obtained the Nobel Prize in 1972 "*for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation*". He made an important contribution showing that after denaturation (a large change of conformation) some proteins fold back spontaneously to their native conformation.

a protein corresponds to the thermodynamic or kinetic minimum.[39] Some experiments indicate the first, others the second possibility.

Despite these complications we generally assume in conformational analysis, that the global minimum and other low-energy conformations play the most important role. In living matter, taking a definite (native) conformation is sometimes crucial. It has been shown[40] that the native conformation of natural enzymes has much lower energy than those of other conformations (energy gap). Artificial enzymes with stochastic amino acid sequences do not usually have this property resulting in no well-defined conformation.

Global molecular mechanics is, in my opinion, one of the most important challenges in chemistry. Students need to look for an important research subject. This is such a subject.[41]

## 7.5 SMALL AMPLITUDE HARMONIC MOTION – NORMAL MODES

The hypersurface $V(\boldsymbol{R})$ has, in general (especially for large molecules), an extremely complex shape with many minima, each corresponding to a stable conformation. Let us choose *one* of those minima and ask *what kind of motion the molecule undergoes, when only small displacements from the equilibrium geometry are allowed*. In addition we assume that the potential energy for this motion is a *harmonic* approximation of the $V(\boldsymbol{R})$ in the neighbourhood of the minimum.[42] Then we obtain the *normal vibrations* or *normal modes*.

> NORMAL MODES
> A normal mode represents a harmonic oscillation (of a certain frequency) of all the atoms of the molecule about their equilibrium positions with the same phase for all the atoms (i.e. all the atoms attain their equilibrium position at the same time).

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[39]It is clear if a protein were denatured very heavily (e.g., cooking chicken soup we could not expect the chicken to return to life).

[40]E.I. Shakanovich, A.M. Gutin, *Proc. Natl. Acad. Sci. USA* 90 (1993) 7195; A. Šali, E.I. Shakanovich, M. Karplus, *Nature* 369 (1994) 248.

[41]My own adventure with this topic is described in L. Piela, "*Handbook of Global Oprimization*", vol. 2, P.M. Pardalos, H.E. Romeijn, eds., Kluwer Academic Publishers, Boston, 2002.

[42]We may note *en passant* that a similar philosophy prevailed in science until quite recent times: take only the linear approximation and forget about non-linearities. It turned out, however, that the non-linear phenomena (cf. Chapter 15) are really fascinating.

The number of such vibrations with non-zero frequencies is equal to $3N - 6$. A vibrational motion of the molecule represents a superposition of these individual normal modes.

## 7.5.1 THEORY OF NORMAL MODES

Suppose we have at our disposal an analytical expression for $V(\boldsymbol{R})$ (e.g., the force field), where $\boldsymbol{R}$ denotes the vector of the Cartesian coordinates of the $N$ atoms of the system (it has $3N$ components). Let us assume (Fig. 7.7) that the function $V(\boldsymbol{R})$ has been minimized in the configurational space, starting from an initial position $\boldsymbol{R}_i$ and going downhill until a minimum position $\boldsymbol{R}_0$ has been reached, the $\boldsymbol{R}_0$ corresponding to one of many minima the $V$ function may possess[43] (we will call the minimum the "closest" to the $\boldsymbol{R}_i$ point in the configurational space). All the points $\boldsymbol{R}_i$ of the configurational space that lead to $\boldsymbol{R}_0$ represent the *basin of the attractor*[44] $\boldsymbol{R}_0$.

*From this time on, all other basins of the function $V(\boldsymbol{R})$ have "disappeared from the theory" – only motion in the neighbourhood of $\boldsymbol{R}_0$ is to be considered.*[45] If someone is aiming to apply harmonic approximation and to consider small displacements from $\boldsymbol{R}_0$ (as we do), then it is a good idea to write down the Taylor expansion of $V$ about $\boldsymbol{R}_0$ [hereafter instead of the symbols $X_1, Y_1, Z_1, X_2, Y_2, Z_2, \dots$ for the atomic Cartesian coordinates we will use a slightly more uniform notation:
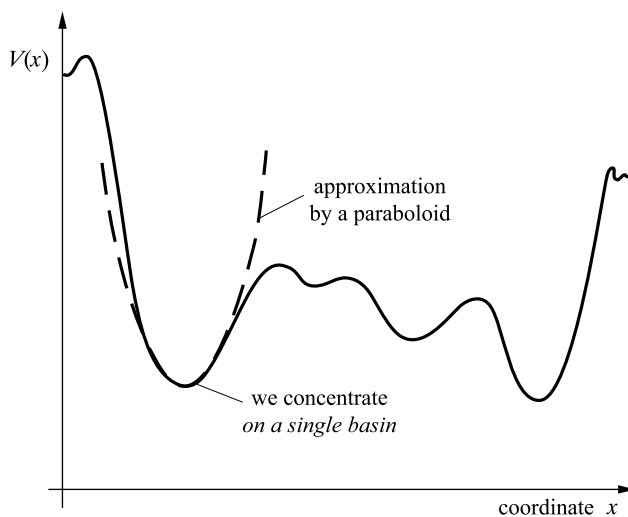


**Fig. 7.7.** A schematic (one-dimensional) view of the hypersurface $V(x)$ that illustrates the choice of a particular basin of $V$ related to the normal modes to be computed. The basin chosen is then approximated by a paraboloid in $3N$ variables. This gives the $3N - 6$ modes with non-zero frequencies and 6 "modes" with zero frequencies.

[43]These are improper minima, because a translation or rotation of the system does not change $V$.

[44]The total configurational space consists of a certain number of such basins.

[45]For another starting conformation $\boldsymbol{R}_i$ we might obtain another minimum of $V(\boldsymbol{R})$. This is why the choice of $\boldsymbol{R}_i$ has to have a definite relation to that which is observed experimentally.

$\boldsymbol{R} = (X_1, X_2, X_3, X_4, X_5, X_6, \ldots, X_{3N})^T]$

$$V(\boldsymbol{R}_0 + \boldsymbol{x}) = V(\boldsymbol{R}_0) + \sum_i \left(\frac{\partial V}{\partial x_i}\right)_0 x_i + \frac{1}{2} \sum_{ij} \left(\frac{\partial^2 V}{\partial x_i \partial x_j}\right)_0 x_i x_j + \cdots, \qquad (7.3)$$

where $\boldsymbol{x} = \boldsymbol{R} - \boldsymbol{R}_0$ is the vector with the *displacements* of the atomic positions from their equilibria ($x_i = X_i - X_{i,0}$ for $i = 1, \ldots, 3N$), while the derivatives are calculated at $\boldsymbol{R} = \boldsymbol{R}_0$.

In $\boldsymbol{R}_0$ all the first derivatives vanish. According to the harmonic approximation, the higher order terms denoted as "$+\cdots$" are neglected. In effect we have

$$V(\boldsymbol{R}_0 + \boldsymbol{x}) \cong V(\boldsymbol{R}_0) + \frac{1}{2} \sum_{ij} \left(\frac{\partial^2 V}{\partial x_i \partial x_j}\right)_0 x_i x_j. \qquad (7.4)$$

In matrix notation we have $V(\boldsymbol{R}_0 + \boldsymbol{x}) = V(\boldsymbol{R}_0) + \frac{1}{2}\boldsymbol{x}^T V'' \boldsymbol{x}$, where $V''$ is a square

force constant    matrix of the Cartesian *force constants*, $(V'')_{ij} = (\frac{\partial^2 V}{\partial x_i \partial x_j})_0$.

The Newton equations of motion for all the atoms of the system can be written in matrix form as ($\ddot{\boldsymbol{x}}$ means the second derivative with respect to time $t$)

$$M\ddot{\boldsymbol{x}} = -V''\boldsymbol{x}, \qquad (7.5)$$

where $M$ is the diagonal matrix of the atomic masses (the numbers on the diagonal are: $M_1, M_1, M_1, M_2, M_2, M_2, \ldots$), because we calculate the force component along the axis $k$ as

$$-\frac{\partial V}{\partial x_k} = -\frac{1}{2} \sum_j \left(\frac{\partial^2 V}{\partial x_k \partial x_j}\right)_0 x_j - \frac{1}{2} \sum_i \left(\frac{\partial^2 V}{\partial x_i \partial x_k}\right)_0 x_i$$

$$= -\sum_j \left(\frac{\partial^2 V}{\partial x_k \partial x_j}\right)_0 x_j = -(V''\boldsymbol{x})_k.$$

We may use the relation $M^{\frac{1}{2}} M^{\frac{1}{2}} = M$

$$M^{\frac{1}{2}} M^{\frac{1}{2}} \ddot{\boldsymbol{x}} = -M^{\frac{1}{2}} M^{-\frac{1}{2}} V'' M^{-\frac{1}{2}} M^{\frac{1}{2}} \boldsymbol{x}, \qquad (7.6)$$

where $M^{\frac{1}{2}}$ is a matrix similar to $M$, but its elements are the square roots of the atom masses instead of the masses, while the matrix $M^{-\frac{1}{2}}$ contains the inverse square roots of the masses. The last equation, after multiplying from the left by $M^{-\frac{1}{2}}$, gives

$$\ddot{\boldsymbol{y}} = -A\boldsymbol{y}, \qquad (7.7)$$

where $\boldsymbol{y} = M^{\frac{1}{2}}\boldsymbol{x}$ and $A = M^{-\frac{1}{2}} V'' M^{-\frac{1}{2}}$.

Let us try to find the solution in the form[46]

$$y = c_1 \exp(+i\omega t) + c_2 \exp(-i\omega t),$$

where the vectors $c_i$ (of the dimension $3N$) of the complex coefficients are time independent. The coefficients $c_i$ depend on the initial conditions as well as on the $A$ matrix. If we say that at time $t = 0$ all the atoms are at equilibrium, i.e. $y(t = 0) = \mathbf{0}$, then we obtain the relation $c_1 = -c_2$ leading to the formula

$$y = L \sin(\omega t), \tag{7.8}$$

where the vector[47] $L$ and $\omega$ depend on the matrix $A$. Vector $L$ is determined only to the accuracy of a multiplication constant, because multiplication of $L$ by any number does not interfere with satisfying (7.7).

When we insert the proposed solution (7.8) in (7.7), we immediately obtain, that $\omega$ and $L$ have to satisfy the following equation

$$(A - \omega^2 \mathbf{1})L = \mathbf{0}. \tag{7.9}$$

The values of $\omega^2$ represent the eigenvalues,[48] while the $L$ are the eigenvectors of the $A$ matrix. There are $3N$ eigenvalues, and each of them corresponds to its eigenvector $L$. This means that we have $3N$ *normal modes*, each mode characterized by its angular frequency $\omega = 2\pi\nu$ ($\nu$ is the frequency) and its vibration amplitudes $L$. Hence, it would be natural to assign a normal mode index $k = 1, \ldots, 3N$ for $\omega$ and $L$. Therefore we have

$$(A - \omega_k^2 \mathbf{1})L_k = 0 \tag{7.10}$$

The diagonalization of $A$ (p. 982) is an efficient technique for solving the eigenvalue problem using commercial computer programs (diagonalization is equivalent to a rotation of the coordinate system, Fig. 7.8).

This is equivalent to replacing $V$ by a $3N$-dimensional paraboloid with origin at $R_0$. The normal mode analysis means such a rotation of the coordinate system as will make the new axes coincide with the principal axes of the paraboloid.

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[46]This form (with $\omega = a + ib$) allows for a constant solution ($a = b = 0$), an exponential growth or vanishing ($a = 0$, $b \neq 0$), oscillations ($a \neq 0$, $b = 0$), oscillatory growing or oscillatory vanishing ($a \neq 0$, $b \neq 0$). For $R_0$ denoting a minimum, $\det A > 0$ and this assures a solution with $a \neq 0$, $b = 0$.

[47]Equal to $2ic_1$, but since $c_1$ is unknown, as for the time being is $L$, therefore we can say goodbye to $c_1$ without feeling any discomfort whatsoever.

[48]$A$ is a symmetric matrix, hence its eigenvalues $\omega^2$ and therefore also $\omega = a + ib$ are real ($b = 0$). Whether $\omega$ are positive, negative or zero depends on the hypersurface $V$ at $R_0$, see Fig. 7.8.
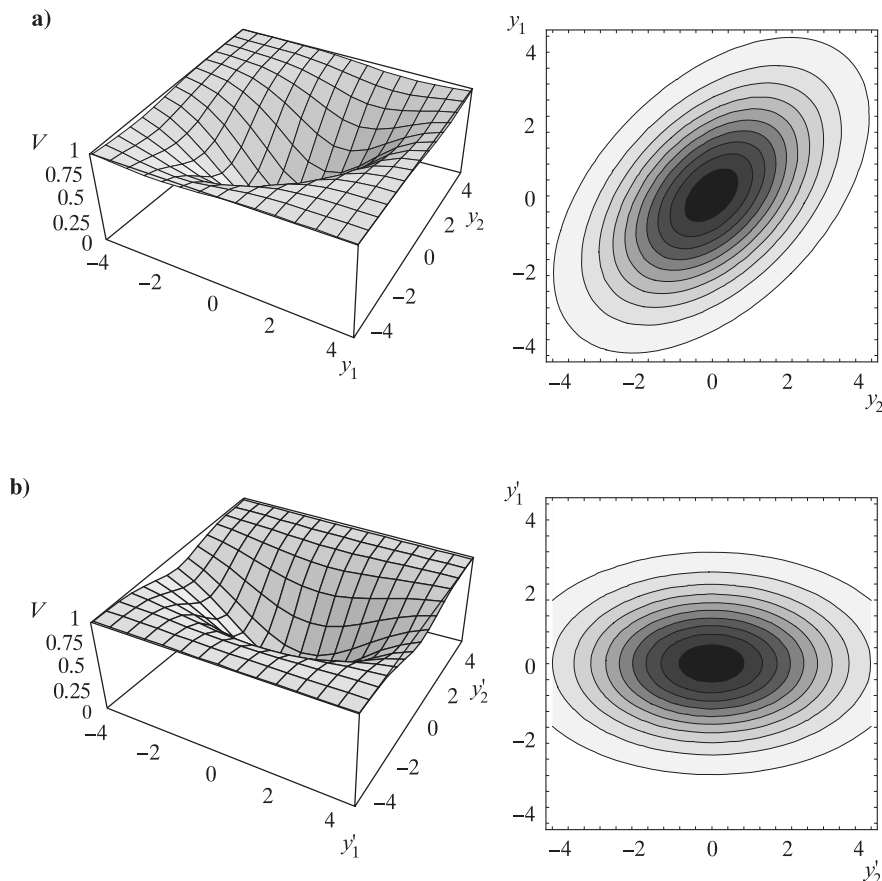
**Fig. 7.8.** (a) and (b) show the normal vibrations (normal modes) about a point $\boldsymbol{R}_0 = \boldsymbol{0}$ being *a minimum* of the potential energy function $V(\boldsymbol{R}_0 + \boldsymbol{y})$ of two variables $\boldsymbol{y} = (y_1, y_2)$. This function is first approximated by a quadratic function, i.e. a paraboloid $\tilde{V}(y_1, y_2)$. Computing the normal modes is equivalent to such a *rotation of the Cartesian coordinate system* (a), that the new axes (b) $y_1'$ and $y_2'$ become the principal axes of any section of $\tilde{V}$ by a plane $\tilde{V} = $ const (i.e. ellipses). Then, we have $\tilde{V}(y_1, y_2) = V(\boldsymbol{R}_0 = \boldsymbol{0}) + \frac{1}{2} k_1 (y_1')^2 + \frac{1}{2} k_2 (y_2')^2$. The problem then becomes equivalent to the two-dimensional harmonic oscillator (cf. Chapter 4) and separates into two independent one-dimensional oscillators (normal modes): one of angular frequency $\omega_1 = 2\pi\nu_1 = \sqrt{\frac{k_1}{m}}$ and the other with angular frequency $\omega_2 = 2\pi\nu_2 = \sqrt{\frac{k_2}{m}}$, where $m$ is the mass of the oscillating particle. Figs. (c), (d) show what would happen, if $\boldsymbol{R}_0$ corresponded not to a minimum, but to a maximum (c) or the saddle point (d). For a maximum (c) $k_1$ and $k_2$ in $\tilde{V}(y_1', y_2') = V(\boldsymbol{0}) + \frac{1}{2} k_1 (y_1')^2 + \frac{1}{2} k_2 (y_2')^2$ would be both *negative*, and therefore the corresponding normal "vibrations" would have had both imaginary frequencies, while for the saddle point (d) only one of the frequencies would be imaginary.

There will be six frequencies (five for a linear molecule) equal to zero. They are connected to the translation and rotation of the molecule in space: three translations along $x, y, z$ and three rotations about $x, y, z$ (two in the case of a linear
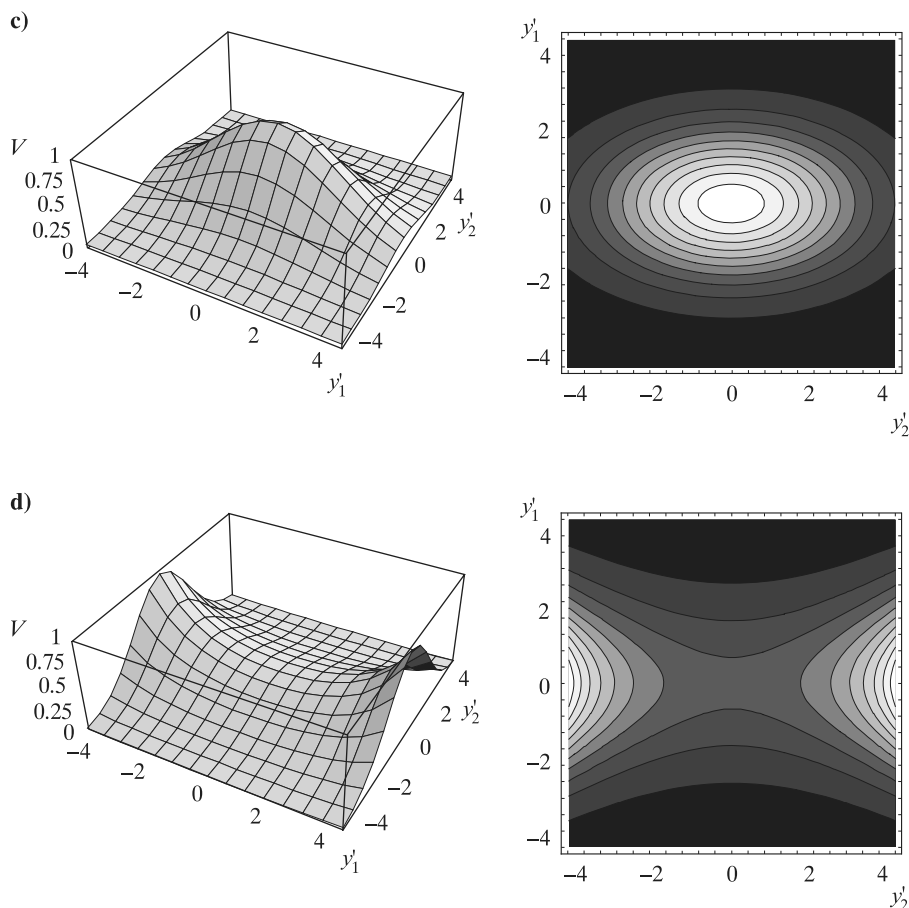
**c)**



**d)**



**Fig. 7.8.** *Continued.*

molecule). Such free translations/rotations do not change the energy and may be thought therefore to correspond to zero force constants.

If we are interested in what the particular atoms are doing, when a single mode $l$ is active, then the displacements from the equilibrium position as a function of time are expressed as

$$x_l = M^{-\frac{1}{2}} y_l = M^{-\frac{1}{2}} L_l \sin(\omega_l t). \tag{7.11}$$

A given atom participates in all vibrational modes. Even if any vibrational mode makes all atoms move, some atoms move more than others. It may happen that a particular mode changes mainly the length of *one of the chemical bonds (stretching mode)*, another mode moves another bond, another changes a particular *bond angle (bending mode)*, etc.

**Table 7.1.** Characteristic frequencies (wave numbers, in $cm^{-1}$) typical for some chemical bonds (stretching vibrations) and bond angles (bending vibrations). This is of great importance for chemical analysis.

| Bond | Vibration | Wave number |
|------|-----------|-------------|
| C–H | stretching | 2850–3400 |
| H–C–H | bending | 1350–1460 |
| C–C | stretching | 700–1250 |
| C=C | stretching | 1600–1700 |
| C≡C | stretching | 2100–2250 |
| C=O | stretching | 1600–1750 |
| N–H | stretching | 3100–3500 |
| O–H | stretching | 3200–4000 |

> This means that some chemical bonds or some functional groups may have *characteristic* vibration frequencies, which is of great importance for the identification of these bonds or groups in chemical analysis.

characteristic
frequencies

In Table 7.1 typical ("*characteristic*") frequencies for some particular chemical bonds are reported. Note, that high frequencies correspond to light atoms (e.g., hydrogen). The wave numbers $\bar{\nu}$ are defined by the relation

$$\omega = 2\pi\nu = 2\pi\bar{\nu}c, \tag{7.12}$$

wave number

with $c$ being the velocity of light and $\nu$ the frequency. The wave number is the number of the wave lengths covering a distance of 1 cm.

## Example 1. *The water molecule*

The goal behind this example is to elaborate ideas associated with various bonds, their characteristic frequencies, and their applicability in chemical analysis.

The *single water* molecule has $3 \times 3 = 9$ normal modes. Six of them have the angular frequencies $\omega$ equal zero (they correspond to three free translations and three free rotations of the molecule in space). Three normal modes remain, the vectors $x$ of eq. (7.11) for these modes can be described as follows (Fig. 7.9, the corresponding wave numbers have been given in parentheses[49]):

- one of the modes means a *symmetric* stretching of the two OH bonds ($\bar{\nu}_{sym} = 3894$ $cm^{-1}$);

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[49]J. Kim, J.Y. Lee, S. Lee, B.J. Mhin, K.S. Kim, *J. Chem. Phys.* 102 (1995) 310. This paper reports normal mode analysis for potential energy hypersurfaces computed by various methods of quantum chemistry. I have chosen the coupled cluster method (see Chapter 10) CCSD(T) as an illustration.
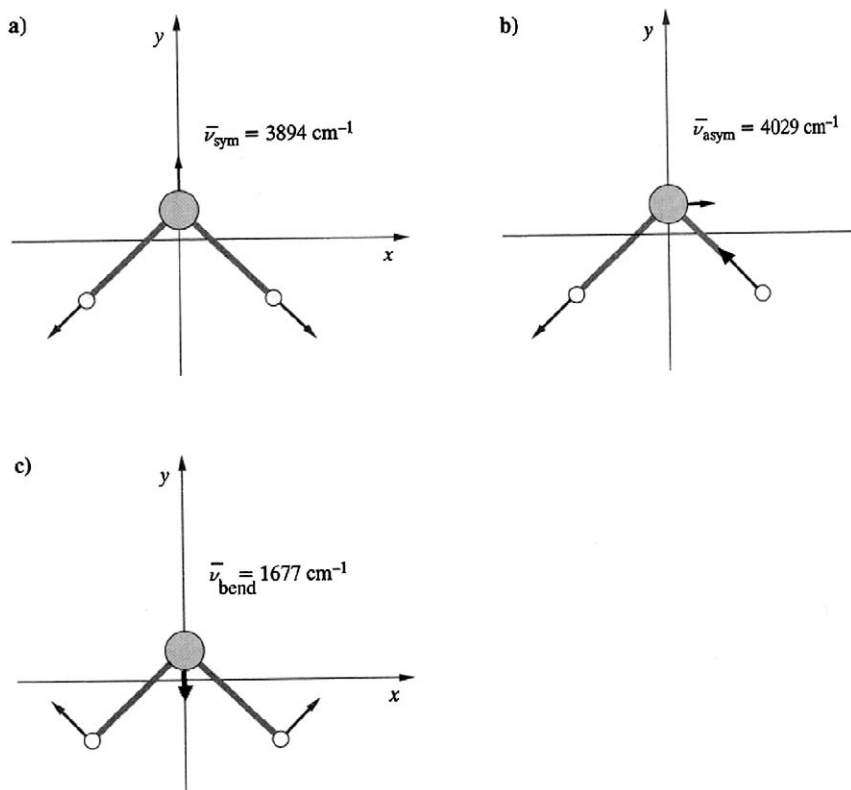
**Fig. 7.9.** The normal modes of the water molecule: (a) symmetric (b) antisymmetric (c) bending.

- the second mode corresponds to a similar, but *antisymmetric* motion, i.e. when one of the bonds shortens the other one elongates and *vice versa*[50] ($\bar{\nu}_{asym} = 4029$ cm$^{-1}$);
- the third mode is called the bending mode and corresponds to an oscillation of the HOH angle about the equilibrium value ($\bar{\nu}_{bend} = 1677$ cm$^{-1}$).

## Example 2. *The water dimer*

Now let us take *two interacting water* molecules. First, let us ask how many minima we can find on the electronic ground-state energy hypersurface. Detailed calculations have shown that there are two such minima (Fig. 7.10). The global minimum corresponds to the configuration characteristic for the *hydrogen bond* (cf. p. 746). One of the molecules is a donor, the other is an acceptor of a proton, Fig. 7.10.a. A local minimum of smaller stability appears when one of the water molecules serves as a donor of two protons, while the other serves as an acceptor of them called the *bifurcated* hydrogen bond, Fig. 7.10.b.

hydrogen bond

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[50] The shortening has the same value as the lengthening. This is a result of the harmonic approximation, in which both shortening and lengthening require the same energy.
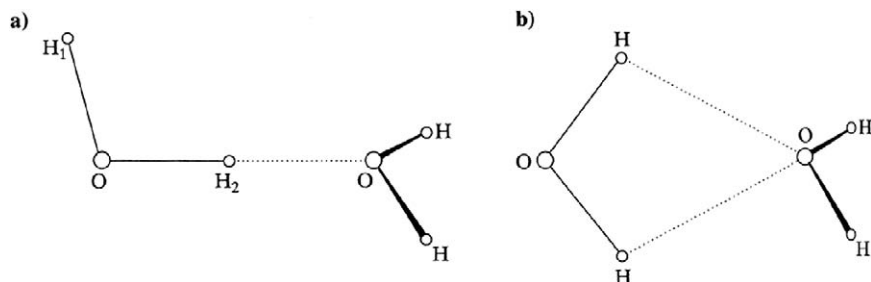
**Fig. 7.10.** The water dimer and the configurations of the nuclei that correspond to minima of the two basins of the potential energy $V$. The global minimum (a) corresponds to a single hydrogen bond O–H...O; the local minimum (b) corresponds to the bifurcated hydrogen bond.

bifurcated
hydrogen bond

    Now, *we decide* to focus on the global minimum potential well. We argue that for thermodynamic reasons, this particular well will be most often represented among water dimers. This potential energy well has to be approximated by a paraboloid. The number of degrees of freedom is equal to $6 \times 3 = 18$ and this is also the number of normal modes to be obtained. As in Example 1, six of them will have zero frequencies and the number of "true" vibrations is 12. This is the number of normal modes, each with its frequency $\omega_k$ and the vector $x_k = M^{-\frac{1}{2}} L_k \sin(\omega_k t)$ that describes the atomic motion. The two water molecules, after forming the hydrogen bond, have not lost their individual features (in other words the OH vibration is *characteristic*). In dimer vibrations we will find the vibration frequencies of individual molecules changed a little by the water–water interaction. These modes should appear in pairs, but the two frequencies should differ (the role of the two water molecules in the dimer is different). The computed frequencies[51] are the following:

- two stretching vibrations with frequencies 3924 cm$^{-1}$ (antisymmetric) and 3904 cm$^{-1}$ (nearly antisymmetric), the higher frequency corresponds to the proton acceptor, the lower to the proton donor;
- two stretching vibrations with frequencies 3796 cm$^{-1}$ (symmetric) and 3704 cm$^{-1}$ (nearly symmetric), again the higher frequency corresponds to the proton acceptor, the lower to the proton donor;
- two bending vibrations with frequencies 1624 cm$^{-1}$ (donor bending) and 1642 cm$^{-1}$ (acceptor bending).

    The proton acceptor has something attached to its heavy atom, the proton donor has something attached to the light hydrogen atom. Let us recall that in the harmonic oscillator, the reduced mass is relevant, which therefore is almost equal to the mass of the *light* proton. If something attaches to this atom, it means a considerable lowering of the frequency. This is why lower frequencies correspond to the proton donor.

    Thus, among 12 modes of the dimer we have discovered six modes which are related to the individual molecules: 4 OH stretching and 2 HOH bending modes.

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[51] R.J. Reimers, R.O. Watts, *Chem. Phys.* 85 (1984) 83.

Now, we have to identify the remaining 6 modes. These are the intermolecular vibrations (Fig. 7.10.a):

- stretching of the hydrogen bond O–H...O (the vibration of two water molecules treated as entities): 183 cm$^{-1}$
- bending of the hydrogen bond O–H...O in the plane of the figure: 345 cm$^{-1}$
- bending of the hydrogen bond O–H...O in the plane perpendicular to the figure: 645 cm$^{-1}$
- rocking of the hydrogen atom H$_1$ perpendicular to the figure plane: 115 cm$^{-1}$
- rocking of the second water molecule (the right-hand side of the figure) in the figure plane: 131 cm$^{-1}$
- rocking of the second water molecule (the right-hand side of the figure) about its symmetry axis: 148 cm$^{-1}$.

As we can see, the intermolecular interactions have made the "intramolecular" vibration frequencies decrease,[52] while the "intermolecular" frequencies have very low frequencies. The last effect is, of course, nothing strange, because a change of intermolecular distances does require a small expenditure of energy (which means small force constants). Note, that the simple Morse oscillator model considered in Chapter 4, p. 175, gave the correct order of magnitude of the intermolecular frequency of two water molecules (235 cm$^{-1}$ as compared to the above, much more accurate, result 183 cm$^{-1}$).

## 7.5.2 ZERO-VIBRATION ENERGY

The computed minimum of $V$ (using any method, either quantum-mechanical or force field) does not represent the energy of the system for exactly the same reason as the bottom of the parabola (the potential energy) does not represent the energy of the harmonic oscillator (cf. the harmonic oscillator, p. 166). The reason is the kinetic energy contribution.

If all the normal oscillators are in their ground states ($v_j = 0$, called the "zero-vibrations"), then the energy of the system is the energy of the bottom of the parabola $V_{\min}$ plus the zero-vibration energy (we assume no rotational contribution)

$$E = V_{\min} + \frac{1}{2} \sum_j (h\nu_j). \tag{7.13}$$

It has been assumed that the vibrations are harmonic in the above formula. This assumption usually makes the frequencies higher by several percent (cf. p. 175).

Taking anharmonicity into account is a much more difficult task than normal mode analysis. Note (Fig. 7.11) that in such a case the position of the minimum

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[52]This is how the hydrogen bonds behave. This, seemingly natural expectation after attaching an additional mass to a vibrating system is legitimate when assuming that the force constants have not increased. An interesting example of the opposite effect for a wide class of compounds has been reported by Pavel Hobza and Zdenek Havlas (P. Hobza, Z. Havlas, *Chem. Rev.* 100 (2000) 4253).
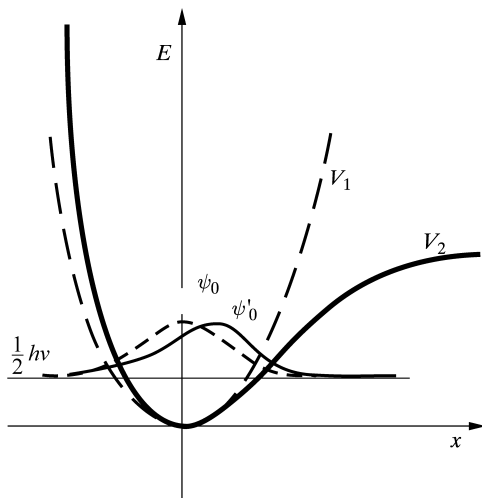
**Fig. 7.11.** The ground-state vibrational wave function $\psi'_0$ of the anharmonic oscillator (of potential energy $V_2$) is *asymmetric and shifted* towards positive values of the displacement when compared to the wave function $\psi_0$ for the harmonic oscillator with the same force constant (the potential energy $V_1$).

of $V$ does not correspond to the mean value of the interatomic distance due to the asymmetry of $V$.

## 7.6 MOLECULAR DYNAMICS (MD)

In all the methods described above there is no such a thing as temperature. It looks as if all the experiments were made after freezing the lab to 0 K. It is difficult to tolerate such a situation.

### 7.6.1 THE MD IDEA

Molecular dynamics is a remedy. The idea is very simple.

If we knew the potential energy $V$ as a function of the position ($\boldsymbol{R}$) of all the atoms (whatever force field has been used for the approximation[53]), then all the forces the atoms undergo could be easily computed. If $\boldsymbol{R} = (X_1, X_2, \ldots, X_{3N})^T$ denotes the coordinates of all the $N$ atoms ($X_1, X_2, X_3$ are the $x$, $y$, $z$ coordinates of atom 1, $X_4, X_5, X_6$ are the $x$, $y$, $z$ of atom 2, etc.), then $-\frac{\partial V}{\partial X_1}$ is the $x$ component of the force atom 1 undergoes, $-\frac{\partial V}{\partial X_2}$ is the $y$ component of the same force, etc. When a force field is used, all this can be easily computed even analytically.[54] We had the identical situation in molecular mechanics, but there we were interested just in making these forces equal to zero (through obtaining the equilibrium geometry). In molecular dynamics we are interested in time $t$, the velocity of the atoms (in this way temperature will come into play) and the acceleration of the atoms.

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[53]Cf. p. 288.

[54]That is, an analytical formula can be derived.

> Our immediate goal is collecting the atomic positions as functions of time,
> i.e. the system trajectory.

The Newton equation tells us that, knowing the force acting on a body (e.g., an atom), we may compute the acceleration the body undergoes. We have to know the mass, but there is no problem with that.[55] Hence the $i$-th component of the acceleration vector is equal to

$$a_i = -\frac{\partial V}{\partial X_i} \cdot \frac{1}{M_i} \tag{7.14}$$

for $i = 1, 2, \ldots, 3N$ ($M_i = M_1$ for $i = 1, 2, 3$, $M_i = M_2$ for $i = 4, 5, 6$, etc.).

Now, let us assume that at $t = 0$ all the atoms have the initial coordinates $\boldsymbol{R}_0$ and the initial velocities[56] $\boldsymbol{v}_0$. Now we assume that the forces calculated act *unchanged* during a short period $\Delta t$ (often 1 femtosecond or $10^{-15}$ s). We know what should happen to a body (atom) if under influence of a constant force during time $\Delta t$. Each atom undergoes a uniformly variable motion and the new position may be found in the vector

$$\boldsymbol{R} = \boldsymbol{R}_0 + \boldsymbol{v}_0\Delta t + \boldsymbol{a}\frac{\Delta t^2}{2}, \tag{7.15}$$

and its new velocity in the vector

$$\boldsymbol{v} = \boldsymbol{v}_0 + \boldsymbol{a}\Delta t, \tag{7.16}$$

where the acceleration $\boldsymbol{a}$ is a vector composed of the acceleration vectors of all the $N$ atoms

$$\boldsymbol{a} = (\boldsymbol{a}_1, \boldsymbol{a}_2, \ldots \boldsymbol{a}_N)^T, \tag{7.17}$$

$$\boldsymbol{a}_1 = \left(-\frac{\partial V}{\partial X_1}, -\frac{\partial V}{\partial X_2}, -\frac{\partial V}{\partial X_3}\right) \cdot \frac{1}{M_1},$$

$$\boldsymbol{a}_2 = \left(-\frac{\partial V}{\partial X_4}, -\frac{\partial V}{\partial X_5}, -\frac{\partial V}{\partial X_6}\right) \cdot \frac{1}{M_2}, \quad \text{etc.}$$

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[55] We assume that what moves is the nucleus. In MD we do not worry about that the nucleus moves together with its electrons. To tell the truth both masses differ only by about 0.05%.

[56] Where could these coordinates be taken from? To tell the truth, almost from a "hat". "Almost" – because some essential things will be assumed. First, we may quite reasonably conceive the geometry of a molecule, because we know which atoms form the chemical bonds, their reasonable lengths, the reasonable values of the bond angles, etc. That is, however, not all we would need for larger molecules. What do we take as dihedral angles? This is a difficult case. Usually we take a conformation, which we could call as "reasonable". In a minute we will take a critical look at this problem. The next question is the velocities. Having nothing better at our disposal, we may use a random number generator, assuring however that the velocities are picked out according to the Maxwell–Boltzmann distribution suitable for a given temperature $T$ of the laboratory, e.g., 300 K. In addition, we will make sure that the system does not rotate or flies off somewhere.

In this way we have our starting position and velocity vectors $\boldsymbol{R}_0$ and $\boldsymbol{v}_0$.

All on the right hand side of (7.15) and (7.16) is known. Therefore the new positions and the new velocities are easy to calculate.[57] Now, we may use the new positions and velocities as a start ones and repeat the whole procedure over and over. This makes it possible to go along the time axis in a step-like way in practice reaching even nanosecond times ($10^{-9}$ sec), which means millions of such steps. The procedure described above simply represents the numerical integration of $3N$ differential equations. If $N = 2000$ then the task is impressive. It is so straightforward, because we are dealing with a numerical (not analytical) solution.[58]

### 7.6.2  WHAT DOES MD OFFER US?

MD trajectory

The computer simulation makes the system evolve from the initial state to the final one. The position $R$ in $3N$-dimensional space becomes a function of time and therefore $R(t)$ represents the *trajectory* of the system in the configurational space. A similar statement pertains to $v(t)$. Knowing the trajectory means that we know the smallest details of the motion of all the atoms. Within the approximations used, we can therefore answer any question about this motion. For example we may ask about some mean values, like the mean value of the total energy, potential energy, kinetic energy, the distance between atom 4 and atom 258, etc. All these quantities may be computed at any step of the procedure, then added up and divided by the number of steps giving the mean values we require. In this way we may obtain the theoretical prediction of the mean value of the interatomic distance and then compare it to, say, the NMR result.

correlation and auto-correlation

In this way we may search for some correlation of motion of some atoms or groups of atoms, i.e. the *space correlation* ("when this group of atoms is shifted to the left, then another group is most often shifted to the right") or the *time correlation* ("when *this* thing happens to the functional group $G_1$, then after a time $\tau$ that most often takes place with another functional group $G_2$") or *time autocorrelation* ("when *this* happens to a certain group of atoms, then after time $\tau$ *the same* most often happens to the same group of atoms"). For example, is the $x$ coordinate of atom 1, i.e. $X_1$ correlated to the coordinate $y$ of atom 41, i.e. $X_{122}$, or are these two quantities absolutely independent? The answer to this question is given by the correlation coefficient $c_{1,122}$ calculated for $M$ simulation steps in the following way:

$$c_{1,122} = \frac{\frac{1}{M} \sum_{i=1}^{M} (X_{1,i} - \langle X_1 \rangle)(X_{122,i} - \langle X_{122} \rangle)}{\sqrt{(\frac{1}{M} \sum_{i=1}^{M} (X_{1,i} - \langle X_1 \rangle)^2)(\frac{1}{M} \sum_{i=1}^{M} (X_{122,i} - \langle X_{122} \rangle)^2)}},$$

where $\langle X_1 \rangle$ and $\langle X_{122} \rangle$ denote the mean values of the coordinates indicated, and the summation goes over the simulation steps. It is seen that any deviation from

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[57]In practice we use a more accurate computational scheme called the *leap frog algorithm*.

[58]By the way, if somebody gave us the force field for galaxies (this is simpler than for molecules), we could solve the problem as easily as in our case. This is what astronomers often do.

independence means a non-zero value of $c_{1,122}$. What could be more correlated to the coordinate $X_1$ than the same $X_1$ (or $-X_1$)? Of course, absolutely nothing. In such a case (in the formula we replace $X_{122,i} \rightarrow X_{1,i}$ and $X_{122} \rightarrow X_1$), we obtain $c_{1,1} = 1$ or $-1$. Hence, $c$ always belongs to $[-1, 1]$, $c = 0$ means independence, $c \pm 1$ means maximum dependence.

Does molecular dynamics have anything to do with reality?

If the described procedure were applied without any modification, then most probably we would have bad luck and our $R_0$ would be located on a slope of the hypersurface $V$. Then, the solution of the Newton equations would reflect what happens to a point (representing the system) when placed on the slope – it would slide downhill. The point would go faster and faster and soon the vector $v$ would not correspond to the room temperature, but, say, to 500 K. Of course, despite such a high temperature the molecule would not disintegrate, because this is not a real molecule but one operating with a force field that usually corresponds to unbreakable chemical bonds. Although the molecule will not fall apart,[59] such a large $T$ has nothing to do with the temperature of the laboratory. This suggests that after some number of steps we should check whether the atomic velocities still correspond to the proper temperature. If not, it is recommended to scale all the velocities by multiplying them by such a factor in order to make them corresponding again to the desired temperature. For this reason, the only goal of the first part of a molecular dynamics simulation is called the "thermalization", in which the error connected to the non-zero $\Delta t$ is averaged and the system is forced stepwise (by scaling) to behave as what is called the canonical ensemble. The canonical ensemble preserves the number of molecules, the volume and the temperature (simulating contact with a thermostat at temperature $T$). In such a "thermalized" system total energy fluctuations are allowed.

thermalization

canonical ensemble

The thermalization done, the next (main) stage of molecular dynamics, i.e. the harvesting of data (trajectory) begins.

### 7.6.3  WHAT TO WORRY ABOUT?

- During simulation, the system has to have enough time to wander through all parts of the phase space[60] that are accessible in the experimental conditions (with which the simulation is to be compared). We are never sure that it happens. We have to check whether the computed mean values depend upon the simulation time. If they do not, then very probably everything is all right – we have a description of the equilibrium state.
- The results of the MD (the mean values) should not depend on the starting point, because it has been chosen arbitrarily. This is usually satisfied for small molecules and their collections. For large and flexible molecules we usually start

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[59]This pertains to a single molecule bound by chemical bonds; a system of several molecules could fall apart.

[60]The Cartesian space of all atomic positions and momenta.

from the vector $R_0$ found from X-ray determined atomic positions. Why? Because *after* the MD we will still stay close to this (all in all experimental) conformation. If the simulation started from another conformation, it would result in a conformation close to this new starting point. This is because even with the most powerful computers, simulation times are too short. In such a way we have a simulation of one conformation evolution rather than a description of the thermodynamic equilibrium.

• The simulation time in the MD is limited on one side by the power of computers and on the other side by the time step $\Delta t$, which is not infinitesimally small, and creates an error that cumulates during the simulation (as a result the total energy may vary too much and the system may be heading into non-physical regions of the phase space).

### 7.6.4 MD OF NON-EQUILIBRIUM PROCESSES

The thermalization is not always what we want. We may be interested in what happens, when a DNA molecule being anchored to a solid surface by one of its end functional groups is distorted by pulling the other end of the molecule. Such MD results may nowadays be compared to the corresponding experiment.

And yet another example. A projectile hits a wall. The projectile is being composed of Lennard-Jones atoms (with some $\varepsilon_p$ and $r_{e,p}$, p. 287), we assume the same for the wall (for other values of the parameters, let us make the wall less resistant than the projectile: $\varepsilon_w < \varepsilon_p$ and $r_{e,w} > r_{e,p}$). Altogether we may have hundreds of thousands or even millions of atoms (i.e. millions of differential equations to solve). Now, we prepare the input $R_0$ and $v_0$ data. The wall atoms are assumed to have stochastic velocities drawn from the Maxwell–Boltzmann distribution for room temperature. The same for the projectile atoms, but additionally they have a constant velocity component along the direction pointing to the wall. At first, nothing particularly interesting happens – the projectile flies towards the wall with a constant velocity (while all the atoms of the system vibrate). Of course, the time the projectile hits the wall is the most interesting. Once the front part of the projectile touches the wall, the wall atoms burst into space in a kind of eruption, the projectile's tip loses some atoms as well, the spot on the wall hit by the projectile vibrates and sends a shock wave and concentric waves travelling within the wall. A violent (and instructive) movie.

Among more civil applications, we may think of the interaction of a drill and a steel plate, to plan better drills and better steel plates, as well as about other micro-tools which have a bright future.

### 7.6.5 QUANTUM-CLASSICAL MD

A typical MD does not allow for breaking bonds and the force fields which allow this give an inadequate, classical picture, so a quantum description is sometimes

a must. The systems treated by MD are usually quite large, which excludes a full quantum-mechanical description.

For enzymes (natural catalysts) researchers proposed[61] joining the quantum and the classical description by making the precision of the description dependent on how far the region of focus is from the enzyme active centre (where the reaction the enzyme facilitates takes place). They proposed dividing the system (enzyme + solvent) into three regions:

- region I represents the active centre atoms,
- region II is the other atoms of the enzyme molecule,
- region III is the solvent.

Region I is treated as a quantum mechanical object and described by the proper time-dependent Schrödinger equation, region II is treated classically by the force field description and the corresponding Newton equations of motion, region III is simulated by a continuous medium (no atomic representation) with a certain dielectric permittivity.

The regions are coupled by their interactions: quantum mechanical region I is subject to the external electric field produced by region II evolving according to its MD as well as that of region III, region II feels the charge distribution changes region I undergoes through electrostatic interaction.

## 7.7 SIMULATED ANNEALING

The goal of MD may differ from simply calculating some mean values, e.g., we may try to use MD to find regions of the configurational space for which the potential energy $V$ is particularly low.[62] From a chemist's point of view, this means trying to find a particularly stable structure (conformation of a single molecule or an aggregate of molecules). To this end, MD is sometimes coupled with an idea of Kirkpatrick et al.,[63] taken from an ancient method of producing metal alloys of exceptional quality (the famous steel of Damascus), and trying to find the minima of arbitrary functions.[64] The idea behind simulated annealing is extremely simple.

This goal is achieved by a series of heating and cooling procedures (called the simulation protocol). First, a starting configuration is chosen that, to the best of our knowledge, is of low energy and the MD simulation is performed at a high temperature $T_1$. As a result, the system (represented by a point $R$ in the configuration space) rushes through a large manifold of configurations $R$, i.e. wanders over

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[61] P. Bała, B. Lesyng, J.A. McCammon, in "*Molecular Aspects of Biotechnology: Computational Methods and Theories*", Kluwer Academic Publishers, p. 299 (1992). A similar philosophy stands behind the Morokuma's ONIOM procedure: M. Svensson, S. Humbel, R.D.J. Froese, T. Matsubara, S. Sieber, K. Morokuma, *J. Phys. Chem.* 100 (1996) 19357.

[62] Like in global molecular mechanics.

[63] S. Kirkpatrick, C.D. Gellat Jr., M.P. Vecchi, *Science* 220 (1983) 671.

[64] I recommend a first-class book: W.H. Press, B.P. Flannery, S.A. Teukolsky, W.T. Vetterling, *Numerical Recipes The Art of Scientific Computing*, Cambridge Univ. Press, Cambridge.

a large portion of the hypersurface $V(\mathbf{R})$. Then, a lower temperature $T_2$ is chosen and the motion slows down, the visited portion of the hypersurface shrinks and hopefully corresponds to some regions of low values of $V$ – the system is confined in a large superbasin (the basin composed of individual minima basins). Now the temperature is raised to a certain value $T_3 < T_1$, thus allowing the system eventually to leave the superbasin and to choose another one, maybe of lower energy. While the system explores the superbasin, the system is cooled again, this time to temperature $T_4 < T_2$, and so forth. Such a procedure does not give any guarantee of finding the global minimum of $V$, but there is a good chance of getting a configuration with much lower energy than the start. The method, being straightforward to implement, is very popular. Its successes are spectacular, although sometimes the results are disappointing. The highly prized swords made in ancient Damascus using annealing, prove that the metal atoms settle down in quasi-optimal positions forming a solid state of low energy – very difficult to break or deform.

## 7.8  LANGEVIN DYNAMICS

In the MD we solve Newton equations of motion for all atoms of the system. Imagine we have a large molecule in an aqueous solution (biology offers us important examples). We have no chance to solve Newton equations because there are too many of them (a lot of water molecules). What do we do then? Let us recall that we are interested in the macromolecule, the water molecules are interesting only

Paul Langevin (1872–1946), French physicist, professor at the College de France. His main achievements are in the theory of magnetism and in relativity theory. His PhD student Louis de Broglie made a breakthrough in quantum theory.

as a medium that changes the conformation of the macromolecule. The changes may occur for many reasons, but the simplest is the most probable – just the fact that the water molecules in their thermal motion hit the atoms of the macromolecule. If so, their role is reduced to a source of chaotic strikes. The main idea behind Langevin dynamics is to ensure that the atoms of the macromolecule indeed feel some random hits from the surrounding medium *without taking this medium into consideration explicitly. This is the main advantage of the method*.

A reasonable part of this problem may be incorporated into the Langevin equation of motion:

$$M_i \ddot{X}_i = -\frac{\partial V}{\partial X_i} + F_i - \gamma_i M_i \dot{X}_i, \qquad (7.18)$$

for $i = 1, 2, \ldots, 3N$, where besides the force $-\nabla V$ resulting from the potential energy $V$ for the macromolecule alone, we also have an additional stochastic force $\mathbf{F}$, whose magnitude and direction are drawn keeping the force related to the temperature and assuring its isotropic character. The coefficient $\gamma_i$ is a friction coefficient and the role of friction is proportional to atomic velocity.

The Langevin equations are solved in the same way as those of MD, with the additional stochastic force drawn using a random number generator.

## 7.9 MONTE CARLO DYNAMICS

Las Vegas, Atlantic City and Monte Carlo are notorious among upright citizens for day and night use of such random number generators as billiards, roulette or cards. Because of this, the idea and even the name of Monte Carlo has been accepted in mathematics, physics, chemistry and biology. The key concept is that a random number, when drawn successively many times, may serve to create a sequence of system snapshots.

All this began from an idea of the mathematician from Lwów, then in Poland (now Lviv in the Ukraine) Stanisław Marcin Ulam.

Perhaps an example will best explain the Monte Carlo method. I have chosen the methodology introduced to the protein folding problem by Andrzej Koliński

Stanisław Ulam (1909–1984), first associated with the University of Lwów, then professor at the Harvard University, University of Wisconsin, University of Colorado, Los Alamos National Laboratory. In Los Alamos Ulam solved the most important bottleneck in hydrogen bomb construction by suggesting that pressure is the most important factor and that sufficient pressure could be achieved by using the *atomic* bomb as a detonator. Using this idea and an idea of Edward Teller about further amplification of the ignition effect by implosion of radiation, both scholars designed the hydrogen bomb. They both own the US patent for H-bomb production.

According to the *Ulam Quarterly Journal* (http://www.ulam.usm.edu/editor.html), Ulam's contribution to science includes logic, set theory, measure theory, probability theory, computer science, topology, dynamic systems, number theory, algebra, algebraic and arithmetic geometry, mathematical biology, control theory, mathematical economy and mathematical physics. He developed and coined the name of the Monte Carlo method, and also the cellular automata method (described at the end of this Chapter). Stanisław Ulam wrote a very interesting autobiography "*Adventures of a Mathematician*".

The picture below shows one of the "magic places" of international science, the *Szkocka Café*, Akademicka street, Lwów, now a bank at Prospekt Szewczenki 27, where, before the World War II, young Polish mathematicians, among them the mathematical genius Stefan Banach, made a breakthrough thereafter called the "Polish school of mathematics".

and Jeffrey Skolnick.[65] In a version of this method we use a simplified model of the real protein molecule, a polymer composed of monomeric peptide units . . . HN– CO–CHR–. . . , as a chain of point-like entities HN–CO–CH from which protrude points representing various side chains R. The polymer chain goes through the vertices of a crystallographic lattice (the side chain points can also occupy only the lattice vertices), which excludes a lot of unstable conformations and enable us to focus on those chemically relevant. The lattice representation speeds computation by several orders of magnitude.

The reasoning goes as follows. The non-zero temperature of the water the protein is immersed in makes the molecule acquire random conformations all the time. The authors assumed that a given starting conformation is modified by a series of random micro-modifications. The micro-modifications allowed have to be chosen so as to obey three rules, these have to be:

- chemically/physically acceptable;
- always local, i.e. they have to pertain to a small fragment of the protein, because in future we would like to simulate the kinetics of the protein chain (how a conformational change evolves);
- able to transform any conformation into any other conformation of the protein.

This way we are able to modify the molecular conformation, but we want the protein to move, i.e. to have the *dynamics* of the system, i.e. a sequence of molecular conformations, each one derived from the previous one in a physically acceptable way.

To this end we have to be able to write down the energy of any given conformation. This is achieved by giving the molecule an energy award if the configuration corresponds to intramolecular energy gain (e.g., trans conformation, the possibility of forming a hydrogen bond or a hydrophobic effect, see Chapter 13), and an energy penalty for intramolecular repulsion (e.g., cis conformation, or when two fragments of the molecule are to occupy the same space). It is, in general, better if the energy awards and penalties have something to do with experimental data for final structures, e.g., can be deduced from crystallographic data.[66]

Now we have to let the molecule move. We start from an arbitrarily chosen conformation and calculate its energy $E_1$. Then, a micro-modification, or even a series of micro-modifications (this way the calculations go faster), is drawn from the micro-modifications list and applied to the molecule. Thus a new conformation is obtained with energy $E_2$. Now the most important step takes place. We decide to *accept* or to *reject* the new conformation according to the *Metropolis criterion*,[67]

Metropolis
criterion

[65]J. Skolnick, A. Koliński, *Science* 250 (1990) 1121.

[66]The Protein Data Bank is the most famous. This Data Basis may serve to form what is called the statistical interaction potential. The potential is computed from the frequency of finding two amino acids close in space (e.g., alanine and serine; there are 20 natural amino acids) in the Protein Data Bank. If the frequency is large, we deduce an attraction has to occur between them, etc.

[67]N. Metropolis, A.W. Rosenbluth, M.N. Rosenbluth, A.H. Teller, E. Teller, *J. Chem. Phys.* 21 (1953) 1087.

which gives the probability of the acceptance as:

$$P_{1 \to 2} = \begin{cases} 1 & \text{if } E_2 \leqslant E_1, \\ a = \exp\left(-\frac{(E_2 - E_1)}{k_B T}\right) & \text{if } E_2 > E_1. \end{cases}$$

Well, we have a *probability* but what we need is a clear decision: *to be or not to be in state* 2. This is where the Monte Carlo spirit comes in, see Fig. 7.12. By using a random number generator we draw a random number $u$ from section $[0, 1]$ and... compare it with the number $a$. If $u \leqslant a$, then we accept the new conformation, otherwise conformation 2 is rejected (and we forget about it). The whole procedure is repeated over and over again: drawing micro-modifications $\to$ a new conformation $\to$ comparison with the old one by the Metropolis criterion $\to$ accepting (the new conformation becomes the current one) or rejecting (the old conformation remains the current one), etc.

The Metropolis criterion is one of those mathematical tricks a chemist has to know about. Note that the algorithm always accepts the conformation 2 if $E_2 \leqslant E_1$ and therefore will have a tendency to lower the energy of the current conformation. On the other hand, when $E_2 > E_1$ the algorithm may decide to increase the energy by accepting the higher energy conformation 2. If $\frac{(E_2 - E_1)}{k_B T} > 0$ is small, the algorithm accepts the new conformation very easily (Fig. 7.12.a), at a given $E_2 - E_1$ the easier the higher the temperature. On the other hand, an attempt at a very high jump (Fig. 7.12.b) in energy may be successful in practice only at very high temperatures. The algorithm prefers higher energy conformations to the same extent as the Boltzmann distribution. Thus, grinding the mill of the algorithm on and on
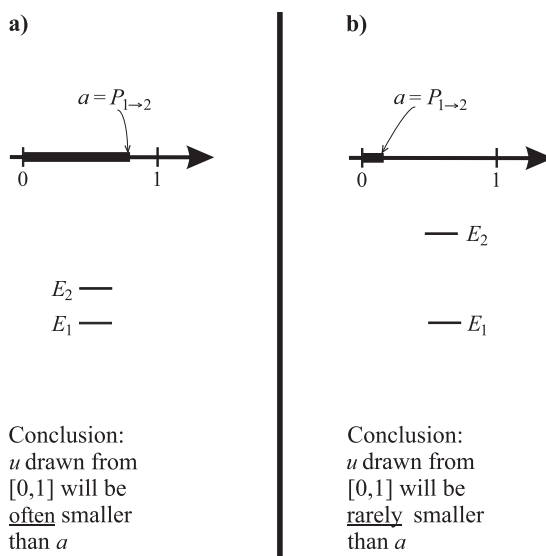


**Fig. 7.12.** Metropolis algorithm. (a) If $E_2$ is only a little higher than $E_1$, then the Metropolis criterion often leads to accepting the new conformation (of energy $E_2$). (b) On the other hand if the energy difference is large, then the new conformation is accepted only rarely. If the temperature increases, the acceptance rate increases too.

Conclusion: $u$ drawn from $[0,1]$ will be <u>often</u> smaller than $a$

Conclusion: $u$ drawn from $[0,1]$ will be <u>rarely</u> smaller than $a$

(sometimes it takes months on the fastest computers of the world) and calculating statistics of the number of accepted conformations as a function of energy, we arrive at the Boltzmann distribution as it should be in thermodynamic equilibrium.

Thus as the mill grinds we can make a film. The film would reveal how the protein molecule behaves at high temperature: the protein acquires practically any new conformation generated by the random micro-modifications and it looks as if the molecule is participating in a kind of rodeo. However, we decide the temperature. Thus let us decide to lower the temperature. Until a certain temperature we will not see any qualitative change in the rodeo, but at a sufficiently low temperature we can recognize that something has happened to the molecule. From time to time (time is proportional to the number of simulation steps) some local structures typical of the secondary structures of proteins (the $\alpha$-helices and the zig-zag type $\beta$-strands, the latter like to bind together laterally by hydrogen bonds) emerge and vanish, emerge again etc.

> When the temperature decreases, at a certain critical value, $T_{crit}$, all of a sudden a stable structure emerges (an analog of the so called native structure, i.e. the one ensuring the molecule can perform its function in nature).

critical
temperature

The structure vibrates a little, especially at the ends of the protein, but further cooling does not introduce anything new. The native structure exhibits a unique secondary structure pattern along the polymeric chain (i.e. definite sections of the $\alpha$ and $\beta$ structures) which packs together into a unique *tertiary structure*. In this way a highly probable scenario for the coil-globular *phase transition* was demonstrated for the first time by Koliński and Skolnick. It seems that predicting the 3D structure of globular proteins uniquely from the sequence of amino acids (an example is shown in Fig. 7.15[68]), will be possible in the near future.

coil-globular
transition

## 7.10  CAR–PARRINELLO DYNAMICS

Despite the fact that the present textbook assumes that the reader has completed a basic quantum chemistry course, the author (according to his declaration in the Introduction) does not profit from this very extensively. Car–Parrinello dynamics is an exception. It positively belongs to the present chapter, while borrowing heavily from the results of Chapter 8. If the reader feels uncomfortable with this, this section may just be omitted.

We have already listed some problems associated with the otherwise nice and powerful MD. We have also mentioned that the force field parameters (e.g., the net atomic charges) do not change when the conformation changes or when two mole-

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[68]This problem is sometimes called "the second genetic code" in the literature. This name reflects the final task of obtaining information about protein function from the "first genetic code" (i.e. DNA) information that encodes protein production.

cules approach, whereas everything has to change. Car and Parrinello[69] thought of a remedy in order to make the parameters change "in flight".

Let us assume the one-electron approximation.[70] Then the total electronic energy $E_0^0(\boldsymbol{R})$ is (in the adiabatic approximation) not only a function of the positions of the nuclei, but also a functional of the spinorbitals $\{\psi_i\}$: $V = V(\boldsymbol{R}, \{\psi_i\}) \equiv E_0^0(\boldsymbol{R})$.

> The function $V = V(\boldsymbol{R}, \{\psi_i\})$ will be minimized with respect to the positions $\boldsymbol{R}$ of the nuclei and the spinorbitals $\{\psi_i\}$ depending on the electronic coordinates.

If we are going to change the spinorbitals, we have to take care of their orthonormality at all stages of the change.[71] For this reason Lagrange multipliers appear in the equations of motion (Appendix N). We obtain the following set of Newton equations for the motion of $M$ nuclei

$$M_I \ddot{X}_I = -\frac{\partial V}{\partial X_I} \quad \text{for } I = 1, \dots, 3M$$

and an equation of motion for each spinorbital (each corresponding to the evolution of one electron probability density in time)

$$\mu \ddot{\psi}_i = -\hat{F}\psi_i + \sum_{j=1}^{N} \Lambda_{ij}\psi_j, \quad i = 1, 2, \dots, N, \tag{7.19}$$

where $\mu > 0$ is a *fictitious parameter*[72] for the electron, $\hat{F}$ is a Fock operator (see Chapter 8, p. 341), and $\Lambda_{ij}$ are the Lagrange multipliers to assure the orthonormality of the spinorbitals $\psi_j$.

Both equations are quite natural. The first (Newton equation) says that a nucleus has to move in the direction of the force acting on it $(-\frac{\partial V}{\partial X_I})$ and the larger the force and the smaller the mass, the larger the acceleration achieved. Good! The left hand side of the second equation and the first term on the right hand side say the following: let the spinorbital $\psi_i$ change in such a way that the orbital energy has a tendency to go down (in the sense of the mean value). How on earth does this follow from the equations? From a basic course in quantum chemistry (this will be repeated in Chapter 8) we know, that the orbital energy may be computed as the mean value of the operator $\hat{F}$ with the spinorbital $\psi_i$, i.e. $\langle \psi_i | \hat{F} \psi_i \rangle$. To focus our attention, let us assume that $\delta\psi_i$ is localized in a small region of space (see Fig. 7.13).

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[69]R. Car, M. Parrinello, *Phys. Rev. Letters* 55 (1985) 2471.

[70]The approximation will be described in Chapter 8 and consists of assuming the wave function in the form of a single Slater determinant built of orthonormal spinorbitals. Car and Parrinello gave the theory for the density functional theory (DFT). As will be seen in Chapter 11, a single determinant function is also considered.

[71]Because the formulae they satisfy are valid under this condition.

[72]We may call it "mass". In practical applications $\mu$ is large, usually taken as a few hundreds of the electron mass, because this assures the agreement of theory and experiment.
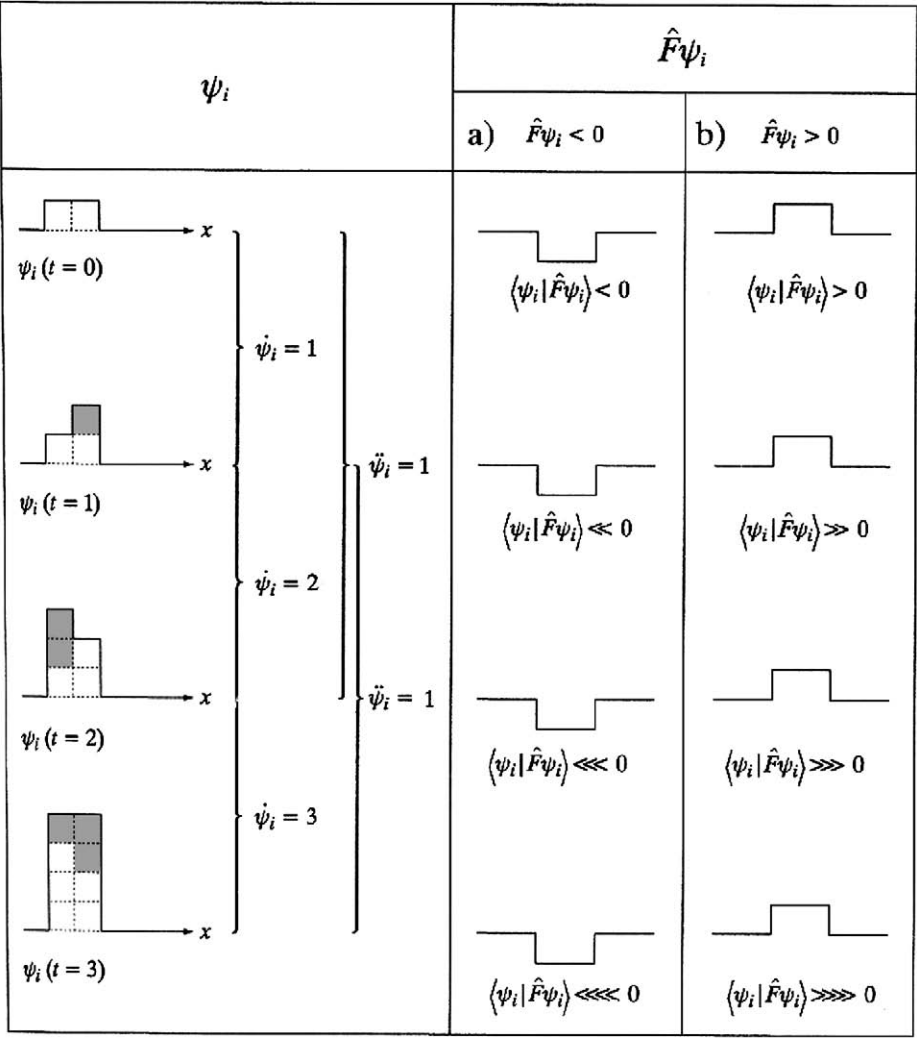
**Fig. 7.13.** A scheme showing why the acceleration $\ddot{\psi}_i$ of the spinorbital $\psi_i$ has to be of the same sign as that of $-\hat{F}\psi_i$. Time (arbitrary units) goes from up ($t = 0$) downwards ($t = 3$) where the time step is $\Delta t = 1$. On the left hand side the changes (localized in 1D space, $x$ axis) of $\psi_i$ are shown in a schematic way (in single small square units). It is seen that the velocity of the change is not constant and the corresponding acceleration is equal to 1. Now let us imagine for simplicity that function $\hat{F}\psi_i$ has its non-zero values precisely where $\psi_i \neq 0$ and let us consider two cases: a) $\hat{F}\psi_i < 0$ and b) $\hat{F}\psi_i > 0$. In such a situation we may easily foresee the sign of the mean value of the energy $\langle\psi_i|\hat{F}\psi_i\rangle$ of an electron occupying spinorbital $\psi_i$. In situation a) the conclusion for changes of $\psi_i$ is: *keep that way* or, in other words, even *increase* the acceleration $\ddot{\psi}_i$ making it proportional to $-\hat{F}\psi_i$. In b) the corresponding conclusion is: *suppress* these changes or in other words *decrease the acceleration* e.g., making it negative as $-\hat{F}\psi_i$. Thus, in *both* cases we have $\mu\ddot{\psi}_i = -\hat{F}\psi_i$, which agrees with eq. (7.19). In both cases there is a trend to lower orbital energy $\varepsilon_i = \langle\psi_i|\hat{F}\psi_i\rangle$.

From Fig. 7.13, it is seen that it would be desirable to have the acceleration $\ddot{\psi}_i$ with the same sign as $-\hat{F}\psi_i$. This is equivalent to increase the changes that lower the corresponding orbital energy, and to suppress the changes that make it higher. The $\psi_i$ spinorbitals obtained in the numerical integration have to be corrected for orthonormality, as is assured by the second term in (7.19).

The prize for the elegance of the Car–Parrinello method is the computation time, which allows one to treat systems currently up to a few hundreds of atoms (while MD may even deal with a million of atoms). The integration interval has to be decreased by a factor of 10 (i.e. 0.1 fs instead of 1 fs), which allows us to reach simulation times of the order of 10–100 picoseconds instead of (in classical MD) nanoseconds.

## 7.11  CELLULAR AUTOMATA

Another powerful tool for chemists is the cellular automata method invented by John (in his Hungarian days Janos) von Neumann[73] and Stanisław Marcin Ulam (under the name of "cellular spaces"). The cellular automata are mathematical models in which space and time both have a granular structure (similar to Monte Carlo simulations on lattices, in MD only time has such a structure). A cellular automaton consists of a periodic lattice of cells (nodes in space). In order to describe the system locally, we assume that every cell has its "state" representing a vector of $N$ components. Each component is a Boolean variable, i.e. a variable having a logical value (e.g., "0" for "*false*" and "1" for "*true*").

A cellular automaton evolves using some *propagation and collision (or actualization) rules* that are always of a *local character*. The local character means that (at a certain time step $t$ and a certain cell) the variables change their values depending only on what happened at *the* cell and at its *neighbours* at time step $t-1$. The propagation rules dictate what would happen next (for each cell) with variables on the cell and on the nearest neighbour cells for each cell independently. But this may provoke a collision of the rules, because a Boolean variable on a cell may be forced to change by the propagation rules related to two or more cells. We need a unique decision and this comes from the collision, or actualization, rules.

For physically relevant states, the propagation and collision rules for the behaviour of such a set of cells as time goes on, may mirror what would happen with a physical system. This is why cellular automata are appealing. Another advantage is that due to the locality mentioned above, the relevant computer programs may be effectively parallelized, which usually significantly speeds up computations. The most interesting cellular automata are those for which the rules are of a non-linear character (cf. Chapter 15).
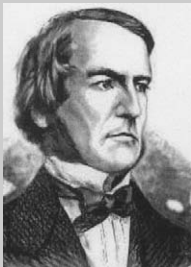
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[73]His short biography is in Chapter 6.

## Example 3. *Gas lattice model*

One of the simplest examples pertains to a lattice model of a gas. Let the lattice be regular two-dimensional (Fig. 7.14).

*Propagation rules*:

There are a certain number of point-like particles of equal mass which may occupy the nodes (cells) only and have unit velocities pointing either in North–South

George Boole (1815–1864), British mathematician and logician. Despite the fact that he was self-taught, he became professor of Mathematics at Queen's College in Cork and a member of the Royal Society. In 1854 Boole wrote his Opus Magnum "*An Investigation of the Laws of Thought*", creating a domain of mathematical logic. The logic was treated there as a kind of algebra.

or East–West directions, thus reaching the next row or column after a unit of time. We assign each cell a state which is a four-dimensional vector of Boolean variables. The first component tells us whether there is a particle moving North on the node (Boolean variables take 0 or 1), the second moving East, the third South and the fourth West. There should be no more than one particle going in one direction at the node, therefore a cell may correspond to 0, 1, 2, 3, 4 par-

ticles. Any particle is shifted by one unit in the direction of the velocity vector (in unit time).

*Collision rules*:

If two particles are going to occupy the same state component at the same cell, the two particles are annihilated and a new pair of particles is created with drawn
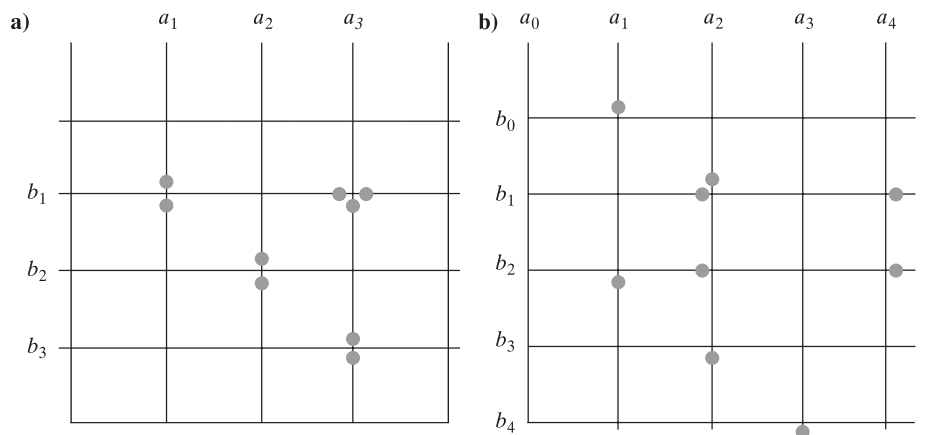


**Fig. 7.14.** Operation of a cellular automaton – a model of gas. The particles occupy the lattice nodes (cells). Their displacement from the node symbolizes which direction they are heading in with the velocity equal to 1 length unit per 1 time step. On the left scheme (a) the initial situation is shown. On the right scheme (b) the result of the one step propagation and one step collision is shown. Collision only take place in one case (at $a_3b_2$) and the collision rule has been applied (of the lateral outgoing). The game would become more dramatic if the number of particles were larger, if the walls of the box as well as the appropriate propagation rules (with walls) were introduced.

positions and velocities. Any two particles which meet at a node with opposite velocities acquire the velocities that are opposite to each other and perpendicular to the old ones (the "lateral outgoing", see Fig. 7.14).

This primitive model has nevertheless an interesting property. It turns out that such a system attains a thermodynamic equilibrium state. No wonder that this approach with more complex lattices and rules became popular. Using the cellular automata we may study an extremely wide range of phenomena, such as turbulent flow of air along a wing surface, electrochemical reactions, etc. It is a simple and powerful tool of general importance.

## Summary

- A *detailed* information about a molecule (in our case: a three atom complex C...AB) may be obtained making use of the potential energy hypersurface for the nuclear motion computed as the ground-state electronic energy (however, even in this case simplified: the AB distance has been frozen). After constructing the basis functions appropriate for the 5 variables and applying the Ritz method of solving the Schrödinger equation we obtain the rovibrational levels and corresponding wave functions for the system. This allows us to compute the IR and microwave spectrum, and as it turns out, this agrees very well with the experimental data, which confirms the high quality of the hypersurface and of the basis set used.
- We may construct an approximation to the potential energy hypersurface for the motion of the nuclei by designing what is called a *force field*, or a simple expression for the electronic energy as a function of the position of the nuclei. Most often in proposed force fields we assume harmonicity of the chemical bonds and bond angles ("springs"). The hypersurface obtained often has a complex shape with many local minima.
- *Molecular mechanics* (should have the adjective "local") represents
  - choice of the starting configuration of the nuclei (a point in the configuration space),
  - sliding slowly downhill from the point (configuration) to the "nearest" local minimum, which corresponds to a stable conformation with respect to small displacements in the configurational space.
- *Global molecular mechanics* means
  - choice of the starting configuration of the nuclei,
  - finding the global (the lowest-energy) minimum, i.e. the most stable configuration of the nuclei.

While the local molecular mechanics represents a standard procedure, the global one is still *in statu nascendi*.

- Any of the potential energy minima can be approximated by a paraboloid. Then, for $N$ nuclei, we obtain $3N - 6$ *normal modes* (i.e. harmonic and having the same phase) of the molecular vibrations. This represents important information about the molecule, because it is sufficient to calculate the IR and Raman spectra (cf. p. 903). Each of the normal modes makes all the atoms move, but some atoms move more than others. It often happens that a certain mode is dominated by the vibration of a particular bond or functional group and therefore the corresponding frequency is *characteristic* for this bond or functional group, which may be very useful in chemical analysis.

- Molecular mechanics does not involve atomic kinetic energy, *molecular dynamics* (MD) does. MD represents a method of solving the Newton equations of motion[74] for all the atoms of the system. The forces acting on each atom at a given configuration of the nuclei are computed (from the potential energy $V$ assumed to be known[75]) as $\boldsymbol{F}_j = -\nabla_j V$ for atoms $j = 1, 2, \ldots, N$. The forces known, we calculate the acceleration vector, and from that the velocities and the new positions of the atoms after a unit time. The system starts to evolve, as time goes on. Important ingredients of the MD procedure are:
  - choice of starting conformation,
  - choice of starting velocities,
  - thermalization at a given temperature (with velocity adjustments to fulfil the appropriate Maxwell–Boltzmann distribution),
  - harvesting the system trajectory,
  - conclusions derived from the trajectory.
- In MD (also in the other techniques listed below) there is the possibility of applying a sequence (protocol) of cooling and heating periods in order to achieve a low-energy configuration of the nuclei (*simulated annealing*). The method is very useful and straightforward to apply.
- Besides MD, there are other useful techniques describing the motion of the system:
  - Langevin dynamics that allows the surrounding solvent to be taken into account, inexpensively.
  - Monte Carlo dynamics – a powerful technique basing on drawing and then accepting/rejecting random configurations by using the *Metropolis criterion*. The criterion says that if the energy of the new configuration is lower, the configuration is accepted, if it is higher, it is accepted with a certain probability.
  - Car–Parrinello dynamics allows for the electron structure to be changed "in flight", when the nuclei move.
  - cellular automata – a technique of general importance, which divides the total system into cells. Each cell is characterized by its state being a vector with its components being Boolean variables. There are propagation rules that change the state, as time goes on, and collision rules, which solve conflicts of the propagation rules. Both types of rules have a local character. Cellular automata evolution may have many features in common with thermodynamic equilibrium.

## Main concepts, new terms

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[74]We sometimes say: integration.

[75]Usually it is a force field.

## From the research front

The number of atoms taken into account in MD may nowadays reach a million. The real problem is not the size of the system, but rather its complexity and the wealth of possible structures, with too large a number to be investigated. Some problems may be simplified by considering a quantum-mechanical part in the details and a classical part described by Newton equations. Another important problem is to predict the 3D structure of proteins, starting from the available amino acid sequence. Every two years from 1994 a CASP (Critical Assessment of techniques for protein Structure Prediction) has been organized in California. CASP is a kind of scientific competition, in which theoretical laboratories (knowing only the amino acid sequence) make blind predictions about 3D protein structures about to be determined in experimental laboratories, see Fig. 7.15. Most of the theoretical methods are based on the similarity of the sequence to a sequence from the Protein Data Bank of the 3D structures, only some of the methods are related to chemical-physics.[76]
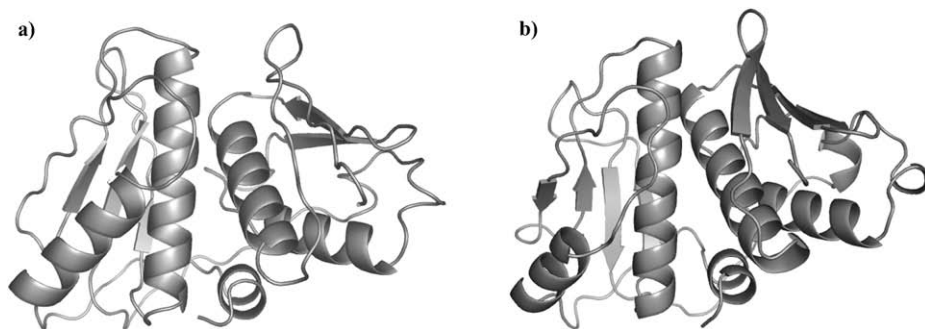


**Fig. 7.15.** One of the target proteins in the 2004 CASP6 competition. The 3D structure (in ribbon representation) obtained for the putative nitroreductase, one of the 1877 proteins of the bacterium *Thermotoga maritima*, which lives in geothermal marine sediments. The energy expression which was used in theoretical calculations takes into account the physical interactions (such as hydrogen bonds, hydrophobic interactions, etc., see Chapter 13) as well as an empirical potential deduced from representative protein experimental structures deposited in the Brookhaven Protein Data Bank (no bias towards the target protein). The molecule represents a chain of 206 amino acids, i.e. about 3000 heavy atoms. Both theory (CASP6 blind prediction) and experiment (carried out within CASP6 as well) give the target molecule containing five $\alpha$-helices and two $\beta$-pleated sheets (wide arrows). These secondary structure elements interact and form the unique (native) tertiary structure, which is able to perform its biological function. (a) predicted by A. Kolinski (to be published) by the Monte Carlo method, and (b) determined experimentally by X-ray diffraction. Both structures in atomic resolution differ (rms) by 2.9 Å. Reproduced by courtesy of Professor Andrzej Koliński.

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[76]More details, e.g., in http://predictioncenter.llnl.gov/casp6/Casp6.html

**Ad futurum...**

The maximum size of the systems investigated by the MM and MD methods will increase systematically to several million atoms in the near future. A critical problem will be the choice of the system to be studied as well as the question to be asked. Very probably non-equilibrium systems will become more and more important, e.g., concerning impact physics, properties of materials subject to various stresses, explosions, self-organization (see Chapter 13), and first of all chemical reactions. At the same time the importance of MD simulations of micro-tools of dimensions of tens of thousands Å will increase.

**Additional literature**

A.R. Leach, "Molecular Modelling. Principles and Applications", Longman, 1996.
  A "Bible" of theoretical simulations.

M.P. Allen, D.J. Tildesley, "Computer Simulations of Liquids", Oxford Science Publications, Clarendon Press, Oxford, 1987.
  A book with a more theoretical flavour.

**Questions**

1. A three-atomic system C...AB with the Hamiltonian

$$\hat{H} = -\frac{\hbar^2}{2\mu R^2}\frac{d}{dR}R^2\frac{d}{dR} + \frac{\hat{l}^2}{2\mu R^2} + \frac{\hat{j}^2}{2\mu_{AB}r_{eq}^2} + V.$$

The symbols $R, r_{eq}, \hat{j}^2$ denote:
a) $R = CA$ distance, $r_{eq} = AB$ distance, $\hat{j}^2$ operator of the square of the angular momentum of C with respect to the centre of mass of AB;
b) $R = AB$ distance, $r_{eq} =$ distance of C from the centre of mass of AB, $\hat{j}^2$ operator of the square of the angular momentum of C with respect to the centre of mass of AB;
c) $R =$ distance of C from the centre of mass of AB, $r_{eq} = AB$ distance, $\hat{j}^2$ operator of the square of the angular momentum of AB with respect to the centre of mass of AB;
d) $R =$ distance of C from the centre of mass of AB, $r_{eq} = AB$ distance, $\hat{j}^2$ operator of the square of the angular momentum of C with respect to the centre of mass of AB.

2. A force field represents an approximation to:
a) the ground-state electronic energy as a function of nuclear configuration; b) vibrational wave function as a function of nuclear configuration; c) potential energy of nuclear repulsion; d) electric field produced by the molecule.

3. Frequencies of the normal modes:
a) pertain to a particular potential energy minimum and correspond to a quadratic dependence of the potential on the displacement from the equilibrium; b) do not depend on the local minimum; c) take into account a small anharmonicity of the oscillators; d) are identical to $H_2$ and HD, because both PESs are identical.

4. The Lennard-Jones potential corresponds to

$$V = \varepsilon\left[\left(\frac{r_0}{r}\right)^{12} - 2\left(\frac{r_0}{r}\right)^6\right],$$

where:

a) $\varepsilon$ is the dissociation energy, $r_0$ is the well depth of $V$; b) $(\frac{dV}{dr})_{r=r_0} = -\varepsilon$; c) $\varepsilon$ represents the dissociation energy, $r_0$ is the distance for which $V = 0$; d) $\varepsilon$ is the well depth, $r_0$ is the position of the minimum of $V$.

5. In equation $(A - \omega_k^2 \mathbf{1})L_k = \mathbf{0}$ for the normal modes ($M$ is the diagonal matrix of the atomic masses):

   a) $\omega_k^2$ may be imaginary; b) $\omega_k^2$ represents an eigenvalue of $M^{-\frac{1}{2}} V'' M^{-\frac{1}{2}}$, where $V''$ is the Hessian computed at the minimum of the potential energy; c) the vector $L_k$ is the $k$-th column of the Hessian $V''$; d) $\omega_k$ is an eigenvalue of $M^{-\frac{1}{2}} V'' M^{-\frac{1}{2}}$, where $V''$ is the Hessian computed in the minimum of the potential energy.

6. The most realistic set of the wave numbers (cm$^{-1}$) corresponding to vibrations of the chemical bonds: C–H, C–C, C=C, respectively, is:
   a) 2900, 1650, 800; b) 800, 2900, 1650; c) 1650, 800, 2900; d) 2900, 800, 1650.

7. The goal of the simulated annealing in MD is:
   a) to lower the temperature of the system; b) to find the most stable structure; c) to adjust the atomic velocities to the Maxwell–Boltzmann distribution; d) thermalization for a given temperature.

8. In the Metropolis algorithm within the Monte Carlo method (for temperature $T$) a new configuration is accepted:
   a) on condition that its energy is higher; b) always; c) always, when its energy is lower, and sometimes when its energy is higher; d) only when its energy is higher than $kT$.

9. In the Langevin MD the solvent molecules:
   a) are treated on the same footing as the solute molecules; b) cause a resistance to the molecular motion and represent a source of random forces; c) cause a resistance to the molecular motion and represent the only source of forces acting on the atoms; d) cause a friction proportional to the acceleration and represent a source of random forces.

10. In Car–Parrinello dynamics:
    a) when the nuclei move the atomic net charges change; b) we minimize the conformational energy in a given force field; c) nuclei and electrons move according to the same equations of motion; d) nuclei move while the electronic charge distribution is "frozen".

## Answers

1c, 2a, 3a, 4d, 5b, 6d, 7b, 8c, 9b, 10a