# 9 Molecular Dynamics Simulations in Biology, Chemistry and Physics

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**Abstract.** We review recent progress in understanding fundamental processes in biology, chemistry and physics on the basis of ab initio and molecular dynamics simulations. The first step of the visual process involving the excitation of bovine rhodopsin after absorption of light is taken as an example from biochemistry to demonstrate what is nowadays possible to simulate numerically. The act of freezing of water has recently been simulated, for the first time successfully, by scientists from chemistry. Martensitic transformation in bulk and nanophase materials, a typical and hitherto not completely solved problem from solid state physics, is used to illustrate the achievements of multimillion atoms simulations.

# 9.1 Molecular Dynamics as a Multidisciplinary Numerical Tool

Molecular dynamics (MD) has proved to be an optimum numerical recipe applicable to problems with many degrees of freedom from quite different fields of science. The knowledge of the energy or potential landscape of interacting particles, like electrons and atoms, enables one to calculate the forces acting on the particles and to study the evolution of the system with time. As long as classical mechanics is appropriate to describe the dynamics of the individual constituents (i.e. atoms or molecules), the Newtonian equations of motion can be related to the statistical mechanics of the (classical) particles by using the equipartition theorem, i.e. by combining the equations

$$m_i \ddot{\mathbf{r}}_i = \mathbf{F}_i, \tag{9.1}$$

$$0 = \frac{3}{2}Nk_BT - \left\langle \sum_i \frac{1}{2}m_i \dot{\mathbf{r}}_i^2 \right\rangle \tag{9.2}$$

for  $i = 1 \dots N$  particles. Although the equipartition theorem holds only for classical particles, to the authors' knowledge the combination of classical and statistical physics has also been used to simulate small molecules at low temperatures without critically discussing so far the limitations of 9.1 and 9.2 when applying to very small quantum mechanical systems. The forces in 9.1 are then simply related to the gradients of the potential energy surface (PES) of either the classical or the quantum mechanical N-particle system. For pedagogical reasons let us recall the classical constant-temperature case. Omitting the statistical average in 9.2 means that the temperature is a measure of the instantaneous kinetic energy in the system (isokinetic simulation) and the equations of motions to be solved are [9.1]

$$m_i \mathbf{\ddot{r}}_i = \mathbf{F}_i - \left(\frac{\sum_j \mathbf{F}_j \mathbf{\dot{r}}_j}{\sum_j m_j \mathbf{\dot{r}}_j^2}\right) m_i \mathbf{\dot{r}}_i, \tag{9.3}$$

which are derived from 9.1 and 9.2 by applying the Gaussian principle of least mean square action, hence the name "Gaussian thermostat". It is to note that the friction-like term in 9.3 is deterministic and gives rise to timereversal invariant trajectories.

Using a different approach Nosé reproduced the canonical phase-space distribution, so that the kinetic energy can fluctuate with a distribution proportional to

$$\exp\left(-\frac{1}{\beta}\sum_{i}\frac{\mathbf{p}_{i}^{2}}{2m_{i}}\right).$$
(9.4)

The canonical distribution is generated with deterministic and time-reversal invariant trajectories of the Hamiltonian

$$H = \sum_{i} \frac{\mathbf{p}_{i}^{2}}{2m_{i}s^{2}} + (\tilde{N}+1)k_{B}T\ln s + \frac{p_{s}^{2}}{2Q} + V(q)$$
(9.5)

with the time-scale variable s, its conjugate momentum  $p_s$  and the "heat bath mass" Q; N is the number of degrees of freedom. Nosé proved that the microcanonical distribution in the augmented set of variables is equivalent to a canonical distribution of the variables q, p', where p' = p/s are the scaled momenta [9.2]. Although a single harmonic oscillator is not sufficiently chaotic to reproduce the canonical distribution, it is interesting to see the result if the method is applied to it. In this case the result depends on Q: For larger values of Q the trajectories fill in a region between two limiting curves [9.3]. For an N-particle system the results (expectation values, i.e. time averages, of observables) are independent of Q and hence of H, the corresponding method of controlling the temperature during the simulations is called "Nosé-Hoover thermostat". The extension of the method with respect to isobaric (constant pressure) simulations by making use of the virial theorem [9.2] allows to deal with many experimental set-ups, where the experiments can be simulated by using the so-called (NPT) ensemble. Finally for the description of structural changes (for example, of condensed matter materials) fluctuations of the size and geometry of the simulation box can be taken into account by using the Parinello-Rahman scheme [9.4]. For further details like, for example, algorithms to solve the equations of motion or a discussion of the statistical nature of the trajectories, we refer to the literature [9.5].

We close the introductory remarks by mentioning some new trends in connection with molecular dynamics. One advantage of molecular dynamics is that the simulations involve the physical time in contrast to other techniques like Monte Carlo. This, however, limits the time that can be spanned to the pico- or nanosecond range if an integration step of the order of one femtosecond is used. This means that many interesting events like conformational changes of large biomolecules, protein folding, solid state reactions and transformations cannot be followed directly. One possibility to circumvent this difficulty is to rely on hybrid methods like a combination of molecular dynamics and kinetic Monte Carlo, for example, in the simulation of growth processes in solid state physics [9.6]. Another way is to freeze in the rapid oscillations, for example, of light atoms like hydrogen etc. and to retain only the dynamics involved with the heavier constituents. Finally there are new developments under way in many places to find optimum tools for the simulations of rare events which likewise can be done by a subtle modification of the potential function [9.7]. For a separation of different time scales in view of biological systems see also [9.8, 9.9].

Apart from the time problem, the extension to larger length scales is another important challenge which has recently been addressed by coupling the region of atomistic simulations to some effective elastic medium [9.10]. Of particular interest is the problem to extend the size of biological systems playing a role in signal transduction. The present state-of-the-art with respect to such simulations is to describe important reactive parts of the molecules quantum mechanically while the rest is treated by molecular mechanics with empirical potentials. This so-called QM/MM technique, which is based on partitioning the Hamiltonian into

$$H = H_{\rm QM} + H_{\rm MM} + H_{\rm QM-MM},\tag{9.6}$$

allows, for example, to deal with the chromophore of rhodopsin on a quantum mechanical basis, whereas the whole sequence of amino acids of the protein as well as part of the lipid membrane into which the latter is embedded, can be described by model potentials (here  $H_{QM}$  is the Hamiltonian to be treated by ab initio methods,  $H_{\rm MM}$  is the purely classical Hamiltonian to be treated by force field methods and  $H_{\rm QM-MM}$  is the Hamiltonian describing the interaction between the quantum mechanical and classical region). Conceptually this procedure is straightforward, difficulties may arise when trying a rigorous treatment of the coupling of the two regions [9.11]. This mixed QM/MM approach can be extended to describe the dynamics of the first excited singlet state. This was done recently on the basis of using pseudopotentials in the quantum mechanical region and the simulation package AMBER in the MM region [9.12]. We have done alike simulations, in particular for rhodopsin, which will be discussed below. Instead of using pseudopotentials, our method relies on a density-functional based tight-binding approach [9.13], which allows to treat a much larger region quantum mechanically with less computational efforts. In the latter approach the MM region is described by using CHARMM [9.14]. Compared to ab initio quantum chemical approaches, the

latter two methods have the advantage that a relatively large QM region can be treated with sufficient accuracy.

The last remark concerns ground state and excited states properties of a quantum mechanical system in view of the normally used Born-Oppenheimer approximation to separate the dynamics of electrons and atoms. The dynamics of the electrons is then determined by the zero-temperature solution of the corresponding Schrödinger equation for the momentary distribution of atoms, while the atoms can be handled at finite temperatures in the molecular dynamics simulations. While this may be a reasonable approximation when simulating ground-state properties of close-packed metallic systems, its accuracy might be questioned when dealing with excited-state properties of biological systems. In additon the crossover from excited electronic states back to the ground sate requires a complicated mixing of basis sets. Both problems are so far not solved unambigiously. For a discussion of the extension of conventional molecular dynamics for simulations not confined to the Born-Oppenheimer surface we refer to [9.15].

# 9.2 Simulation of Biochemical Systems

In the following we discuss two molecular systems, cyclodextrin interacting with bulk water and the protein rhodopsin with internal water, for which exemplay the molecular simulations help to deepen our understanding of the experimental data being available. We start the discussion with water which is the most abundant substance on earth and the only naturally occuring inorganic liquid. Due to the distinctive properties of  $H_2O$ , its interaction with larger molecules, proteins or even the DNA is in many cases decisive for their properties: In the absence of water (and its hydrogen bonding network) proteins lack activity and the DNA loses its double-helical structure. For recent reviews concerning fundamental aspects of water (from bulk water to biological, internal and surface waters, the phase diagram of ice, etc.) we refer to [9.16-9.19]. The different dynamics of biological water compared to bulk water is, for example, determined by the protein-solvent interaction: Typical consequences are multiple-time-scale processes, time-dependent diffusion coefficients and excess low-frequency vibrational modes (glassy behavior of water, see [9.19]). In the context of methods concentrating on ab initio MD of liquids and applied to water in particular see, for example, [9.20]. Much recent work is connected to the simulation of proton transfer and solvation of ions in water or high pressure ice [9.21–9.24]. This is also of interest with respect to the pH value of different waters affecting organisms living in water  $(pH = -log_{10}[H^+])$ , where  $[H^+]$  is the molar concentration (mol/L); pH ranges from 0 to 14, with 7 being neutral; pHs less than 7 are acidic while pHs greater than 7 are basic; normal rainwater has a pH value of 5.7).

## 9.2.1 Molecular Dynamics Simulation of Liquid Water

Useful tools to sample the structure and dynamics of water are the radial distribution function (RDF), the time correlation functions and diffusion coefficients. Here we briefly discuss results for the RDFs defined by

$$g_{\alpha\beta}(\mathbf{r}) = \frac{1}{\rho^2} \left\langle \sum_{i \neq j} \delta(\mathbf{r}_{i\alpha}) \delta(\mathbf{r}_{j\beta} - \mathbf{r}) \right\rangle, \qquad (9.7)$$

which is related by Fourier transformation to the (intermolecular) structure factor,

$$S_{\alpha\beta}(\mathbf{k}) = 1 + \rho \int d^3 r \, e^{i\mathbf{k}\mathbf{r}} \, \left[g_{\alpha\beta}(\mathbf{r}) - 1\right], \qquad (9.8)$$

where  $\alpha$ ,  $\beta = 0$ , H; *i*, *j* refer to the molecules (note that in the case of  $g_{\text{OH}}$  and  $g_{\text{HH}}$  we have, in addition, intramolecular contributions from i = j); the X-ray data give the O–O pair correlations [9.25] while the neutron data provide all pair correlations including the intramolecular correlations [9.26]);  $\rho = N/V$ , N is the number of water molecules.  $S_{\alpha\beta}(\mathbf{k})$  is directly related to X-ray or neutron scattering intensities.

Figure 9.1 shows calculated RDFs of bulk water obtained from Car-Parrinello (CP) MD simulations [9.27] in comparison to the most recent results of X-ray [9.25] and neutron scattering experiments [9.26]. In the simulations the standard CP method [9.28] has been employed within a plane-wave-basis density functional theory, using the BLYP [9.29] gradientcorrected exchange-correlation energy functional and the norm-conserving Troullier-Martins pseudopotential [9.30] (with a plane-wave cutoff of 80 Ry for the "good" results and  $\Gamma$  point only in the Brillouin sampling; for further details and discussion of previous simulations see [9.27]). There is remarkable agreement of the calculated RDFs with most recent both X-ray [9.25] and neutron [9.26] scattering experiments.

We have checked the RDFs by simulations using two other methods, VASP [9.31] and DFTB [9.13]. For the bulk density of water and room temperature we obtain the same good agreement with experiment as in the CP simulations when using VASP while the DFTB calculations yield a smaller and higher first peak in  $g_{OO}(\mathbf{r})$ . However, the simulations also show that for slightly different densities than bulk density or insufficient system sizes and simulation times position and height of the first peak in  $g_{OO}(\mathbf{r})$  are not so well reproduced. One should also note that with respect to simulations using empirical water models in many cases a relatively high and sharp first peak, contrary to experiments, is obtained [9.25, 9.26] (for a survey of molecular models of water see [9.32]). Thus ab initio MD simulations are very useful to obtain correct information about the structure (and its temperature dependence) of water, they are also useful for the interpretation of the experimental data.



Fig. 9.1. The oxygen-oxygen (top), oxygen-hydrogen (middle) and hydrogenhydrogen (bottom) radial distribution functions obtained from a Car-Parrinello molecular dynamics simulation of a system of 64 H<sub>2</sub>O molecules (solid lines) [9.27] compared to results of neutron diffraction scattering [9.26] (dashed lines). The total simulation time was 11 ps and the average ionic temperature was 307 K. The figure was adapted from [9.27].

Of all the RDFs,  $g_{OO}(\mathbf{r})$  is perhaps the most informative. Calculation of the coordination number defined by

$$N_c = 4\pi\rho \int_{0}^{r_{\rm min}} dr \, r^2 \, g_{\rm OO}(r), \qquad (9.9)$$

(where  $r_{\rm min}$  is the location of the first minimum in  $g_{\rm OO}(r)$ ) gives the number of nearest neighbor water molecules. The recent X-ray data give  $N_c = 4.7$  [9.25] while the CP simulations yield an average number of H<sub>2</sub>O molecules in the first coordination shell of about 4.0. A coordination number  $N_c < 5$  indicates that liquid water preserves much of its tetrahedral, ice-like structuring, while differences from the ice-like structuring can be found from the hydrogen-bonding patterns, see, for example, [9.33]. The ratio of the distances of the first two peak positions in  $g_{\rm OO}(r)$  is about 1.64 close to the ideal value of  $2(2/3)^{1/2} = 1.633$  in an ice Ih-type lattice. The increasing width with increasing distance is an indication of increasing disorder in the liquid. The first two peaks in  $g_{\rm OH}(r)$  and  $g_{\rm HH}(r)$  correspond to the average intramolecular distances of O–H and H–H, respectively. For further discussions we refer to [9.27].

The RDFs of water and ice from 220 to 673 K and at pressures up to 400 MPa have recently been discussed on the basis of neutron scattering data [9.26]. It is interesting to note that in the ice formation there is still substantial disorder in the hydrogen bonding pattern as can be checked from the width of the RDFs. MD simulations of the phase transition, i.e., freezing of water to ice, are more difficult to achieve than melting of ice. There have only been a few successful MD runs of free (i.e., not confined) water which show ice nucleation and subsequent percolation of the nucleus throughout the simulation box containing 512 water molecules [9.34]. Due to the complex global potential-energy surface, a large number of possible network configurations are possible. This causes large structural fluctuations showing up in the simulations hindering the system to find an easy pathway from the liquid to the frozen state (in spite of the fact that water molecules forming tiny ice-like clusters with four-coordinated hydrogen bonds have by 2 kJ/mol lower potential energy than that of other water molecules [9.34]). Results of MD simulations of ice nucleation are shown in Fig. 9.2.

The constant-temperature MD simulations have been done for 512 molecules in the simulation box with a time step of 1 fs. The TIP4P model for water has been employed, which is a flat 4-center model with a potential energy consisting of Coulomb and Lennard-Jones terms, whereby the oxygen charge is shifted to a fourth site located closer but equidistant from the two hydrogen atoms [9.35].

The essential four stages in the freezing process are discussed in detail in [9.34]. The simulations show that the number of six-member rings  $N_{6R}$ fluctuates during the simulations but only increases after an initial nucleus has formed and the ice-growth process has set in, see Fig. 9.2b and following. The authors investigated also the so-called  $Q_6$  parameter [9.36], which may serve to characterize in how far the hydrogen bonds are coherently (icosahedrally) ordered. From the simulations it seems to follow that neither  $N_{6R}$ nor  $Q_6$  are suitable order parameters to describe the entire freezing process. Obviously coherent icosahedral orientational correlations are an imperfect solution to characterize tetrahedral packing of water molecules as in ice [9.36].

The reverse process, melting of ice, is easier to simulate. In the following we briefly present results of melting of water clusters simulated by our group. Numerous studies have been devoted to understand the dynamics of small clusters of water since the beginning of simulation studies in the 1970s and to elucidate the nature of the pseudo-first order melting transition.

Our aim is to simulate the melting of water clusters  $(H_2O)_n$  of selected sizes (shown in Fig. 9.3) and how their properties evolve with size from ab initio type of calculations using the DFTB method [9.37]. Some of the bigger



**Fig. 9.2.** Change of the hydrogen bond network structure of water with the simulation time. During the freezing (for times t > 320 ns) the gradual formation of a perfect honeycomb structure becomes visible (lower panel) accompanied by a considerable decrease of the potential energy or loss of kinetic energy of the water molecules. The MD simulation of water freezing is performed for 512 molecules (with density 0.96 g/cm<sup>3</sup>) in the simulation box with periodic boundary conditions and involves thermalization at a high temperature followed by quenching (at time t = 0) to a low temperature of 230 K (supercooled water). After 256 ns a polyhedral structure consisting of long-lasting hydrogen bonds forms spontaneously acting as an initial nucleus, see the circled region in (b). The lines indicate hydrogen bonds among water molecules. The brightest blue lines are those with hydrogen-bond lifetimes of more than 2 ns. Reprinted by permission from Nature copyright 2002 Macmillan Publishers Ltd. (http://www.nature.com/nature) [9.34].

clusters were modeled from the existing smaller units of n = 3, 4, 5 and 6. The preference is given to those with lowest energy. A fair search for the minima of these structures was carried out before the structures were used as the starting geometry in the MD simulation runs. The results of our simulation are compared with some of the results available for the existing clusters from simulation with a model classical pairwise additive potential (CPAP) [9.38]. We have, however, to point out that results to be found in the literature for the apparent global minimum structures of water clusters differ for some of



**Fig. 9.3.** Initial configuration for some selected  $(H_2O)_n$  clusters. The number of molecules in each of the clusters is indicated by n.

the clusters (compare, for example, the global minmum structures of water clusters calculated using the TIP3P and TIP4P potentials [9.39]). Our final relaxed structures for some of the smaller clusters such as n = 3, 4, 5, 6, 8and 20 are in agreement with some of the relaxed geometries of Wales and Lee [9.38, 9.40, 9.41].

The melting temperature can then be obtained from the inflexion point of the calorific curve (energy versus temperature). However, it is sometimes difficult to see the abrupt change in the energy. Hence, instead Lindemann's criteria of melting (along with the former condition) is used, which is obtained from the root-mean-square bond-length fluctuations  $\delta_{OO}$  of oxygen in each of the clusters as given by

$$\delta_{\rm OO} = \frac{2}{N(N-1)} \sum_{i < j} \frac{\sqrt{\langle r_{ij}^2 \rangle - \langle r_{ij} \rangle^2}}{\langle r_{ij} \rangle},\tag{9.10}$$

where the brackets denote time averages, and  $r_{ij}$  is the distance between the oxygen atoms *i* and *j*. The summation is over all *N* molecules. According to this criterion, melting is caused by a vibrational instability when  $\delta_{OO}$  reaches a critical value. We paid attention of how to define the melting temperature  $T_m$  for a particular cluster. A cluster of water may have different isomeriza-



**Fig. 9.4.** Calculated energy per  $(H_2O)_n$  cluster together with the root mean square fluctuations in the O–O bond lengths versus temperature (n = 3, 4). The vertical dotted lines mark the approximate melting tmperatures.

tion in which there is interconversion of a water cluster from one form of isomer to another when the hydrogen-bond breaking and reforming is substantial, leading to new structures before melting. This behavior shows up as fluctuations in  $\delta_{OO}(T)$ . Figure 9.4 shows the behavior of the energy and of  $\delta_{OO}$  versus temperature for the case of two small clusters.

The size dependence of the melting temperature obtained with the DFTB method compared to calculations using model potentials ([9.38,9.42], a pair-



Fig. 9.5. The melting temperature against the number of water molecules. Both results of our DFTB calculations and simulations using the CPAP [9.38] classical potential are plotted. Also shown is the  $T_m$  value for the pentamer cluster obtained from a point charge model [9.42]. Remarkable are the rather high melting temperatures for the small clusters.

wise additive and point charge model, respectively) is shown in Fig. 9.5. Both calorific curve and Lindemann's criterion from  $\delta_{OO}(T)$  show some agreements in locating  $T_m$ . For some of the clusters it becomes difficult to see clearly the transition point in  $\delta_{OO}(T)$  because of the fluctuations.

### 9.2.2 Simulation of $\beta$ -Cyclodextrin-Binaphtyl and Water

Cyclodextrins are truncated doughnut-shaped cyclic oligosaccharide molecules consisting of  $\alpha$ -1,4 linked D-glucose units with a hydrophobic interior surface and a hydrophilic external surface. The most prominent and abundant of the cyclodextrins are  $\alpha$  ([C<sub>36</sub>H<sub>60</sub>O<sub>30</sub>]),  $\beta$  ([C<sub>42</sub>H<sub>70</sub>O<sub>35</sub>]) and  $\gamma$  ([C<sub>48</sub>H<sub>80</sub>O<sub>40</sub>]) cyclodextrins with six, seven and eight glucose units, respectively. They are produced by degradation of amylose by glucosyltransferases, in which one or several turns of the amylose helix are hydrolysed off and their ends are joined together to form cyclic oligosaccharides called cyclodextrins or cycloamylases. They have the ability to form inclusion compounds, acting as hosts, by allowing other molecules (guests) into their hydrophobic cavity [9.43–9.45]. In various sizes and chemical characteristics they are being used in pharmaceutical chemistry as drug delivery systems, in chromatography and as enzyme catalysis models or assistants in protein folding [9.46].

Of particular interest of these mentioned applications are inclusion of  $\beta$ cyclodextrin (BCD) complexes with organic binaphthyl derivatives (BNP) (2,2'-dihydroxy-1,1'-binaphthyl, a chiral molecule, which exists in an enantiomeric form). We have done structure optimization and MD simulation for one of the enantiomeric pairs (R) of 2,2'-dihydroxyl-1,1'-binaphthyl. The optimization of the complex in the crystalized form without solvent water was first carried out in order to have the initial information about how the complexation pathway should proceed. After this, we solvated the whole complex in water which provides the driving force for the complexation and further stabilization of the complex. The most obvious candidate properties from simulation that might indicate the stability of these complexes are a number of properties that describe the structure over time. One of these is the evolution of the geometry of the guest molecule inside the cavity of the BCD and the formation of the hydrogen-bonded network of the complex. The energy of various trial configurations of the guest molecule inside the cavity of the host as well as geometrical evolution of the guest molecules has been calculated. The role of water as the solvent in the stabilization of the complex is also reported. Details of the simulations are discussed with respect to the UV/Vis and CD spectra in [9.47]. Here we simply present two results.

Figure 9.6 shows the results of structure optimization and MD simulation of BCD in liquid water and the analogous simulation with the binaphtyl guest molecule (the starting geometry for BCD was taken from the Crystallographic Database [9.48]). We have employed the DFTB method which allows to handle such a large number of atoms in reasonable computational time. As the Figure shows, without the guest molecule, the hydrophobic interior of



Fig. 9.6. Left: The relaxed structure of  $\beta$ -cyclodextrin in water (79 water molecules) inside the simulation box of dimension  $25 \times 25 \times 25$  Å<sup>3</sup> from DFTB MD simulations. The inside of  $\beta$ -cyclodextrin is hydrophobic. It can take a maximum of 7 water molecules in equilibrium. Right: The relaxed structure of  $\beta$ -cyclodextrin plus binaphtyl guest molecule in water (119 water molecules) inside the simulation box of dimension  $25 \times 25 \times 25$  Å<sup>3</sup> from DFTB MD simulations. The water inside the hydrophobic cavity of cyclodextrin is easily displaced by an active guest molecule like binaphtyl. The starting geometry for  $\beta$ -cyclodextrin, 'SIBJAO', was taken from the Crystallographic Database [9.48].

BCD can accomodate a maximum of 7 water molecules. This water is easily displaced if an active guest molecule like binaphtyl is used. The most stable conformation of this complex is due to the hydrogen bonding formation of the active agent guest molecule with the torus-like macro ring of the host BCD leading to the formation of the stable adduct in the lipophilic cavity of the biopolimeric matrix.

The role of the solvent, water, in stabilizing the complex becomes obvious from the changes of the structure of water around the complex.

The calculated RDF between the BCD hydroxyl oxygen atoms (OH) and the water atoms reveals the existence of two shells of water molecules around BCD at r = 3.0 and 5.3 Å, respectively, in agreement with the calculation reported in [9.49] using the DLPOLY(2) program. From the calculated RDF between BCD hydroxyl (OH) and glycosidic oxygen atoms we find that in the equilibrium conformation the hydroxyl groups of the BCD molecule link together with the glycosidic oxygens via the formation of hydrogen bonds, as evidenced by the peaks of the RDF.

Furthermore we observe the formation adduct of the host (BCD)-BNP complex with the formation of hydrogen bonding between the hydroxyl group of the BNP and the glycosidic oxygen atoms of BCD as indicated by the first peak in the corresponding RDF at around 2.85 Å. This indicates the presence of biphenyl aromatic rings of binaphtyl inside the hydrophobic cavity of BCD. Water molecules form a network of hydrogen bonds with both the primary and secondary hydroxyl groups.

## 9.2.3 Simulation of Bovine Rhodopsin

Rhodopsin is the visual pigment of the vertebrate rod photoreceptor cells in the retina, which is responsible for light/dark vision. It is composed of the 40-kDa apoprotein opsin (348 amino acids) and its chromophore, 11-*cis*retinal. The retinal is covalently bound to the protein via a protonated Schiff base (pSb) linkage to the side chain of Lys296 [9.50]. Upon illumination of light  $\sim 500$  nm, the chromophore photoisomerizes from 11-cis to all-trans in less than 200 fs [9.51]. This is followed by a conformational change in the protein and after a series of distinct photointermediates has been passed through [9.52–9.54], an active receptor conformation is formed by deprotonation of the Schiff base (Sb), which corresponds spectroscopically to the blueshifted metarhodopsin II (meta-II) with 380 nm absorption maximum [9.55]. This meta-II state allows binding to a G-protein transducin (Gt) to the cytoplasmic surface of the receptor [9.56]. The currently proposed model is shown in Fig. 9.7, although it may not reflect intermediates which have similar absorbance spectra but different protein structures [9.57].



**Fig. 9.7.** The energy landscape of the visual cycle of rhodopsin. A 2.8 Å high-resolution structure is available only for 11-*cis* rhodopsin in the ground state. No high-resolution structures are available for the intermediates. Reprinted by permission from CMLS copyright 1998 Birkhäuser Publishers Ltd. (http://www.birkhauser.ch) [9.57].

Rhodopsin can be isolated from the retina of a number of species [9.58] and it is one of the most extensively studied G-protein-coupled receptors (GPCRs). Bovine eyes are readily available from meat packing plants and are a major source of rhodopsin. Due to the obstacles to obtain three-dimensional crystals, until recently structural data were very limited. A break-through was achieved by Tetsuji Okada who developed an efficient protocol of purifying the protein and using high concentration of zinc led to dissolutions yielding three-dimensional crystals useful for X-ray crystallographic analysis [9.59, 9.60], which allowed a 2.8 Å resolution of the structure [9.61]. This is the first high-resolution structure of a member of the GPCRs family and will trigger a major (re)modeling wave through the entire GPCRs superfamily. Till now three data sets of coordinates of rhodopsin are available from the Brookhaven protein data bank [9.61–9.63].

We report here of ab initio molecular dynamics simulations which are based on one of the new crystal structures (1F88). The new crystal structure has shown that the counterion Glu113 is located somehow near the Sb protonated nitrogen; however, the mechanism of the stability of the proton is not clear from the crystal structure. Using VASP we have investigated the stability of the proton. Our results show that one of the amino acids, Thr94, which stays near the counterion, has, in addition to the stabilizing role of a water molecule, influence on the stability of the protonated state [9.64]. This as well as results for the chromophore in the binding pocket consisting of 27 amino acids [9.65] and results for the whole protein using QM/MM will be briefly discussed in the following.

We note that Lys296 (lysine), to which the chromophore in rhodopsin is attached but otherwise free, and Glu113 (glutamine), the counterion, are two of the key amino acid residues responsible for the structure and function of the retinal chromophore in rhodopsin. Spectroscopy data [9.66] predict that Glu113 is located near C12 of the retinal polyene (upon absortion of light and electronic excitation the chromophore photoisomerizes with a twist around the C12–C13 bond) and the counterion is not directly associated with the protonated Schiff base [9.67]. It is also known that Thr94 (threenine) is an important residue (for example, the mutation of Thr94 can cause night blindness [9.68]). The new crystal structure has revealed that Thr94 is located near the counterion. The results of our MD simulations have shown that the absence of threenine and/or one water molecule makes the protonation state of the chromophore unstable. The calculation was done with VASP for a minimal 1F88 model consisting of 11-cis-retinal pSb, Lys296, Glu112, Thr94 and one water molecule, which results in a protonated state stabilized by a hydrogen-bonding network [9.64].

Calculations for a larger part of the binding pocket (also for the 1F88 structure) were done using the DFTB method. The initial planar geometry of the chromophore is marked by yellow in Fig. 9.9 (the positions of the amino residues of the crystal structure are marked by thin lines) while the resulting optimum geometry of the 6-s-*cis*, 11-*cis*-retinal pSb is marked by



Fig. 9.8. Environment of the 11-*cis*-retinal chromophore. (A) Experimental electron density with 3.3 and (B) with 2.8 Å resolution; (C) shows schematically the side chains around the chromophore while (D) shows the binding pocket of the protein with the amino acids within 4.5 Å distance of the chromophore. Reprinted by permission from Science copyright 2000 AAAS (http://www.sciencemag.org) [9.61].

green (the fully relaxed positions of the amino residues are shown by thick lines). We observe that Thr94 is hydrogen bonded to the oxygen atom of Glu113 in agreement with the previous investigations of the minimal model with VASP. The figure also shows that the  $\beta$ -ionone region is very tightly packed with many aromatic residues.



Fig. 9.9. Overlay of the minimized (green) and initial planar (yellow) structures of the 11-cis-retinal chromophore. Thin and thick lines correspond to the pocket and the minimized conformations and the initial crystal structure [9.61], respectively.

The QM/MM calculations were done with the CHARMM package [9.14] (in which the quantum mechanical region containing the chromophore and part of Lys296 (altogether 60 atoms) was calculated using DFTB, while the outer region, containing the remaining part of the protein, was calculated using the CHARMM force-field method [9.64]). For the connection between the region treated quantum mechanically and the outer region we have used the link atom method: We have cut a single bond of Lys296 between  $C_{\beta}$  and  $C_{\gamma}$  and inserted a dummy hydrogen atom, see Fig. 9.10. The link atom is not seen by the atoms in the classical regions. The entire system with additional water molecules consists of 5578 atoms (348 amino acids with missing residues inserted and 19 water molecules).

Although a quantum mechanical treatment of the entire system would be desirable, it cannot be done in reasonable computer time. In the simulations we used the refined 2.6 Å resolution structure 1L9H of Okada [9.63]. Röhrig *et al.* have also performed MM calculations for the entire protein [9.69], however their conclusion of a deprotonated Glu181 is inconsistent with our results and also contradicts the experimental result [9.70] showing that the protonated state of Glu181 is stable due to the hydrogen bonded network. This hydrogen bonded network extends to the counterion Glu113 and has an important function in the rhodopsin photocycle [9.70]. The stability of the 1L9H structure of rhodopsin was examined by MD simulations using the canonical ensemble and the Nosé thermostat [9.64].



Fig. 9.10. The link of the QM to the MM region which has been used in the calculations of the protein rhodopsin. The link is between the  $C_{\beta}$  and  $C_{\gamma}$  atoms of Lys296, where a dummy hydrogen atom is inserted.

## 9.3 Simulation of Chemical Reactions in the Gas Phase

The study of chemical reactions by using computational methods is of great technological interest because it can provide useful information about details of a reaction which are – at least not yet – feasible in experiment. Today it is often not possible to directly observe a chemical reaction in real time, so experimentalists have often only got information about reactants and products. It is easy to imagine that, if one knew exactly how a reaction proceeded (the 'reaction pathway'), one could optimize the conditions under which reactions occur and increase productivity.

Whereas in conventional transition state theory one can obtain information about activation energies and thereby rate constants of a reaction to high accuracy, ab initio MD allows one to simulate the reaction itself at finite temperature. This immediately provides valuable information about possible reaction pathways. As an example we present results of MD simulations of the abstraction reaction  $SiCl_4 + H \rightleftharpoons SiCl_3 + HCl$ . Due to the high reactivity of the radicals involved this reaction plays an important role in the formation of nano- and microcrystalline silicon films and nanoparticles from gas phase precursor molecules  $SiCl_4$  and  $H_2$ , which are commonly used, for example, in chemical vapor deposition (CVD) processes.

Figure 9.11 shows snapshots from an MD simulation of this reaction. The calculations were performed on the basis of DFT in combination with plane waves and ultrasoft pseudopotentials in periodic boundary conditions using VASP. The exchange correlation energy was calculated by using the generalized gradient approximation in a functional form proposed by Perdew and Wang in 1991 [9.71]. The size of the supercell was  $12 \times 12 \times 20$  Å<sup>3</sup> to ensure that no interaction between atoms and their periodic images occured. To simulate possible reaction conditions, the SiCl<sub>4</sub> molecule was first placed alone into the cell and equilibrated at a temperature of 2000 K. After that the H atom was put into the simulation box at a distance of 6 Å from the nearest Cl atom and given an initial velocity of 0.1 Å/fs in the direction of the



**Fig. 9.11.** Snapshots of an MD simulation of the reaction  $SiCl_4 + H \rightleftharpoons SiCl_3 + HCl$ . The  $SiCl_4$  molecule has been equilibrated at 2000 K. The relative velocity of the reactants is 0.1 Å/fs. The fluctuations of the Si–Cl bonds are clearly visible.

molecule. From the figure one can see that the Si-Cl bonds are first fluctuating around their equilibrium values. When the H atom has reached the molecule, the corresponding Si-Cl bond is elongated (at t = 43 fs). This stretching is increased by the H-Cl interaction and eventually the bond breaks (t = 125 fs), resulting in a SiCl<sub>3</sub> radical and the HCl molecule, which are moving apart (t = 150 fs).

From this simulation we learn that the two relevant parameters of the reaction are the distances between Si–Cl and Cl–H (Cl being the abstracted Cl atom). In Fig. 9.12 a contour plot of the PES of the reaction in terms of these two parameters is shown. Contour lines are drawn at a distance of 100 meV. The energy barrier was calculated to 420 meV, the corresponding transition state (TS) is clearly visible as the saddlepoint in the diagram. Together with the PES the trajectories of MD simulations of the reaction are drawn. The solid line corresponds to the (successful) simulation of which the snapshots are depicted in Fig. 9.11. The other lines belong to simulations, where the starting conditions were only slightly different. The only change was the instantaneous initial velocity of the involved Cl atom. For the solid curve it was 0.004 Å/fs towards the arriving H atom, in case of the curves with the long dashes it was zero (the velocity of the H atom was increased to 0.11 Å/fs for the curve with the dots) and -0.004 Å/fs (away from the H atom) for the curve with the short dashes. The result of this minor change is tremendous: When the Cl atom does not move towards the H atom, the



Fig. 9.12. Potential-energy surface of the reaction  $SiCl_4 + H \rightleftharpoons SiCl_3 + HCl$  in terms of the two relevant parameters, the Si–Cl and Cl–H bond lengths. Contour lines are drawn at a distance of 100 meV. The trajectories of different MD runs are also included. The solid line corresponds to the simulation of which the snapshots are shown in Fig. 9.11. Initial velocities of the scattered Cl atom: 0.004 Å/fs in the direction of the incoming H atom (solid line), 0.0 Å/fs (long-dashed line), -0.004 Å/fs (short-dashed line).

Si–Cl bond is not stretched, when the hydrogen atom has arrived, and the force between the Cl and the H atom is not strong enough to result in the breaking of the Si–Cl bond. The hydrogen atom is then just scattered back, which becomes very clear from the trajectories on the PES. This can also not be changed by increasing the impact velocity, the reaction then just proceeds deeper into the repulsive part of the PES.

We see now that the momentary vibrational state of the  $SiCl_4$  molecule is crucial for the outcome of the reaction, the translational kinetic energy of the reactants is not that decisive. Even if this energy is large enough to overcome the barrier, in many cases the system is not able to cross the TS. This is related to the fact that the TS is located towards the side of the products. Molecular dynamics has once again proved to be a valuable tool in the examination of the bahavior of molecular systems.

# 9.4 Simulation of Structural Transformations in Solids and Particles

As examples from solid state physics we consider successful ab initio calculations and MD simulations of the phase transformations in Fe-Ni and Ni-Mn-Ga alloys. Martensitic instabilities, shape memory and magnetovolume effects in iron-based alloys are of scientific and technological interest. In spite of the large amount of experimental and theoretical work there have remained unsolved problems [9.72]. The Heusler compound Ni<sub>2</sub>MnGa and related alloys also exhibit displacive, diffusionless structural transformations. The Heusler alloys have attracted much interest because in these systems the martensitic transformation occurs below the Curie temperature which leads to magnetic shape-memory effects controllable by an external magnetic field [9.73].

In addition we have considered the crossover from the bulk materials to nanoparticles and have investigated the change of the structural transformation with the size of the particles. As last example we show that the melting of Al clusters depends on the size of the clusters; the simulation yields a smooth melting curve different from the case of melting of water clusters. Scaling of the austenitic/martensitic transformation and melting temperatures with the inverse of the cluster diameter is observed.

## 9.4.1 Simulation of the Phase Diagram of Fe-Ni and Ni-Mn-Ga Alloys

Figures 9.13 and 9.14 show the simulated phase diagrams in comparison to the experimental ones. Early ab initio calculations using the KKR CPA method gave already most of the structure of the theoretical phase diagram for Fe-Ni by plotting energy differences between the phases as a function of the composition [9.74]. Refined KKR CPA calculations give improved results [9.75]. It is remarkable how, for example, the energy differences between the nonmagnetic and magnetic ab initio solutions mimic the temperature variation of the experimental Curie temperature with the composition. Tendencies of the experimental transformation temperatures are also reproduced by the MD simulations [9.76, 9.77] employing the so-called EAM potentials [9.78]. The transformation temperatures are not so well reproduced for compositions near elemental iron, which can be attributed to the fact that the EAM potentials have been built to reproduce the elastic properties of the ferromagnetic ground states of the two elements without construction of an explicit magnetic term, which might be important when varying the temperature from the magnetic ground state to the high-temperature parmamagnetic state in the simulations.

The experimental Ni-Mn-Ga phase diagram has been taken from [9.79] (premartensitic phase transformation) and [9.80] (Curie temperature and



**Fig. 9.13.** Left: The experimental phase diagram showing the Curie temperature  $T_c$  and the magnetization  $M_{\rm FCC}$  of the iron-nickel alloys in the fcc structure.  $A_{\rm S, F}$  and  $M_{\rm S, F}$  denote the experimental austenite and martensite start and final temperatures, respectively, on the iron-rich side. Filled circles: Results of moleculardynamics simulations employing model potentials (upper dots:  $\alpha \rightarrow \gamma$  transition for increasing temperature; lower dots:  $\gamma \rightarrow \alpha$  transition for decreasing temperature [9.76, 9.77]. Right: The theoretical phase diagram showing the energy differences between the nonmagnetic (NM) and ferromagnetic (HS: high spin) ground states,  $E_{\rm NM} - E_{\rm HS}$ , of the alloys in the face centered cubic (fcc) structure and the energy differences between the fcc and body centered cubic (bcc) structures on the ironrich side: Open squares mark single-site KKR CPA calculations by [9.74] and filled squares are results of multi-site KKR CPA calculations by [9.75]. The filled circles are the ab initio results for the magnetic moments.

martensitic transformation). The theoretical phase diagram has been simulated using a phenomenological model based on Ginzburg-Landau theory [9.81–9.83]. Also in this case there is reasonable agreement between experimental and theoretical data.

Detailed ab initio investigations of the vibrational properties using VASP show that, in contrast to the case of Fe-Ni, the Ni-Mn-Ga alloys show pronounced phonon softening [9.84, 9.85] in agreement with experimental data [9.86]. The calculated phonon dispersion relations seem to show that besides Kohn anomalies originating from nesting properties of the Fermi surfaces of minority and majority spin electrons [9.85], hybridization effects involving the optical phonons of Ni and acoustical phonons could give a different explanation for the occurrence of the 3M, 5M and 7M martensitic structures [9.84]. Further *ab inito* simulations are currently performed in order to investigate the important influence of shuffling of atoms on premartensitic and martensitic transformations.



Fig. 9.14. Experimental (left) and theoretical (right) phase diagrams for  $Ni_{2+x}Mn_{1-x}Ga$ . Data for the premartensitic transformation temperature  $T_P$  have been taken from [9.79], data for  $T_c$  and  $T_M$  from [9.80]. The theoretical diagram has been obtained by phenomenological modeling [9.81–9.83]. Thick lines denote phase transformations, thin lines show the boundaries of the stability areas; broad areas (simultaneous stability of two different phases) are around first order phase transitions. L2<sub>1</sub> is the high-temperature austenite structure, 3M the premartensitic structure and T is the tetragonal non-modulated martensitic structure.

# 9.4.2 Simulation of the Structural Transformation in Fe-Ni Particles

We have employed MD simulations using EAM potentials in order to characterize the crossover from the bulk properties of Fe-Ni alloys to the properties of Fe-Ni nanoparticles. Metallic nanoparticles show interesting effects such as systematic changes of elastic and vibrational properties with the size of the particles. Increasing hardness with decreasing grain size due to dislocation immobilization at the grain boundaries (known as Hall-Petch effect) and increasing softness for still smaller sizes due to grain boundary sliding (reverse Hall-Petch effect) have been discussed in the frame of MD simulations for Cu [9.87]. Interestingly Young's modulus or the hardness of the particles scale with the inverse square root of the diameter of the particles [9.88].

Of particular interest are structural transformations in the nanoparticles. Multimillion atoms simulations have shown that perfect spherical Fe-Ni particles without any defects do not undergo a martensitic transformation when cooling the particles from the high temperature fcc phase to low temperatures. This means that the austenitic phase is stable at least during the time of the MD runs and that we do not observe the homogeneous nucleation of martensite. This is in agreement with the experimental observation that the austenite is stabilized in nanometer-sized particles, i.e., there is no doubt that the reduction in size results in the stabilization of austenite [9.89]. Although the same authors speculate that the increase of surface areas with decreasing size and lattice softening (in combination with defects) may enhance the martensitic transformation in nanometer-sized particles.

However, the high-temperature austenitic transformation is observed in the MD simulations. If we prepare the spherical Fe-Ni particles (without defects) at low temperatures in the martensitic structure then we find upon heating the martensitic–austenitic transformation (bcc  $\rightarrow$  fcc). This transformation (in contrast to the reverse fcc  $\rightarrow$  bcc transformation at lower temperature) is entropy driven and seemingly barrierless as simulations of the transformation along the Bain path show [9.77, 9.90]. Of interest is here the change (scaling) of the austenitic transformation temperature with the inverse of the particle diameter shown in Fig. 9.15 for different compositions.



Fig. 9.15. Change of the austenitic transformation temperature with the inverse diameter of the Fe-Ni clusters. The extrapolation of  $d \to \infty$  yields transformation temperatures which lie within the range of experimentally observed austenitic start and final temperatures, see the phase diagram in Fig. 9.13.

In order to observe the heterogeneous nucleation of martensite at defects of the particles we have prepared a simple cubic  $Fe_{80}Ni_{20}$  particle, see Fig. 9.16. The corners of the particle act as defects from which the nucleation starts. The cubic particle was prepared in the austenitic fcc structure; the subsequent MD run consisted of 50.000 integration steps at 50 K covering a time range of 50 ps.

A quantitative picture of the particle dynamics is shown in Fig. 9.17 which gives an impression of the variation of the radial distribution function and of the structure with time. The large-scale MD results were obtained by using the SPaSM code [9.91–9.93] on the parallel SUN machine at Los Alamos.



Fig. 9.16. Nucleation of martensite (bcc: green) at the corners of the cubic  $Fe_{80}Ni_{20}$  particle at a temperature of 50 K, which grows with a fraction of the sound velocity into the austenitic matrix (fcc: red). The growing martensitic regions consist of twins with twin boundaries marked by thin red lines, the formation of which helps to lower the elastic tension.



Fig. 9.17. Variation of the radial distribution function of the cubic  $Fe_{80}Ni_{20}$  particle in Fig. 9.16 at 50 K with time. The transformation from the fcc to the bcc structure is visible from the splitting of the first maximum as time proceeds.

## 9.4.3 Simulation of the Melting of Al Clusters

A description of the process of melting is still a challenging problem of statistical physics. Experimental studies show that undercooling of metallic melts is easily achieved while overheating of the solid phase is usually hindered. This asymmetry is associated with the sudden onset of melting (seemingly without an energetic barrier), whereby the solid "sinks" in its own melt which starts from the surfaces of the solid, while for the liquid-solid transition an energy barrier, associated with the formation of nucleation centers, has to be overcome, see the discussion in [9.94]. Only the suppression of the influence of surface effects leads to overheating phenomena, which, however, is not easily achieved in the experiments, but which can be observed in the simulations when employing periodic boundary conditions in order to minimize the effect of surfaces. Furthermore, the problem to designate an order parameter to the solid-liquid transition is an unsettled problem, since the simulations show that there is a continuous change of more than one single local structural symmetry when, for example, one undercools the melt in the simulations to lower temperatures than the melting temperature. However, it has has recently been emphasized that a five-fold symmetry in the liquid phase of lead might be important for the discussion of general aspects of melting [9.95].

Melting of clusters is of particular interest, since here surface effects are dominant for the small clusters. Moreover, the phenomenological melting theory predicts a scaling of the melting temperature with the inverse of the particle diameter like

$$1 - T_m/T_B \propto 1/d,\tag{9.11}$$

where  $T_m$  and  $T_B$  are the melting temperatures for the cluster and the corresponding bulk material, see, for example, [9.96]. In the MD simulations, when approaching  $T_m$ , we observe increasing structural fluctuations with a sudden first-order like transition to the liquid state in the case of Al clusters. The change of the energy of free Al clusters, simulated by using an optimized EAM potential with the help of ab initio results, with different numbers of atoms is shown in Fig. 9.18. The crossover from the solid to the liquid state is associated with a jump in each curve. From the plot of  $T_m(1/d)$  we observe indeed a behavior as predicted by the above formula. In fact, this curve is rather smooth. The smoothness is surprising in view of the many structural changes the clusters undergo in picoseconds (in the simulations) just before melting. These structural fluctuations due to the enhanced diffusion of the surface atoms before melting also shows up as additional low-frequency distributions to the vibrational density of states of the particles. A common neighbor analysis shows that around the melting temperature different kinds



Fig. 9.18. Change of the energy of free aluminum clusters with different numbers of atoms as a function of the temperature. The sudden change in the energy marks the change from the solid to the liquid phase.

of crystallographic symmetries exist with a dominant fcc contibution in both the solid and liquid states.

On the basis of our simulation results concerning the melting of Al clusters we cannot explain why there are so many oscillations in the experimental melting curve of Na clusters [9.97] (in [9.97] the influence of energy and entropy on the melting of Na clusters is discussed in detail but this cannot explain the oscillation of the melting temperature with the cluster size). We currently employ ab initio MD simulations in order to investigate the melting of Na clusters.

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