ISSN 0027-1314, Moscow University Chemistry Bulletin, 2007, Vol. 62, No. 4, pp. 177–179. © Allerton Press, Inc., 2007.
Original Russian Text © A.A. Moskovskii, I.A. Kaliman, A.V. Akimov, S.S. Konyukhov, B.L. Grigorenko, A.V. Nemukhin, 2007, published in Vestnik Moskovskogo Universiteta. Khimiya, 2007, No. 4, pp. 219–222.

Implementation of a Molecular Dynamics Approach with Rigid Fragments to Simulation of Chemical Reactions in Biomolecular Systems

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Received December 4, 2006

Abstract—We describe a new implementation of the molecular dynamics method aimed at simulation of the properties of biomolecular systems in which chemical reactions are possible. The quantum mechanical/molecular mechanical method based on the effective fragment potential theory is used for calculating the energies and forces along trajectories. Due to specific features of the effective fragment theory, the behavior of the molecular mechanical subsystem is described by rigid body dynamics. The method has been applied to simulation of proton transfer along the chain of water molecules inside the gramicidin channel.

DOI: 10.3103/S0027131407040013

The molecular dynamics (MD) method is a computer experiment aimed at simulation of the behavior of a molecular system in time by means of numerical integration of equations of motion [1, 2]. Most MD calculations are performed in the framework of classical mechanics with the use of empirical potentials of interactions of atoms, so-called force fields. As applied to biomolecular systems [3], the classical MD method makes it possible to solve a large number of important problems, first of all, to simulate conformational transformations of proteins and nucleic acids, but it is inapplicable to the study of chemical transformations in a system. A promising line of development of MD, which is intended for simulation of the cleavage and formation of bonds in a biomolecular system, implies the use of a hybrid quantum mechanics/molecular mechanics method (QM/MM) [4–7] for calculating the energies and forces acting on atoms. In this approach, a relatively small region of the entire system is treated quantum mechanically, whereas the remainder is described using classical force fields.

The practical implementation of a new combined quantum mechanics and molecular dynamics (QM/MD) method, in which the forces calculated in the quantum subsystem by quantum-chemical algorithms are processed by MD software and, together with classical forces, permit the calculation of the trajectories of all particles in the system, is rather sophisticated and only a few attempts to solve this problem have been made [8].

In the present work, we describe the implementation of a QM/MD approach in which the energies and energy gradients are calculated by the QM/MM method based on the effective fragment potential theory [6, 7, 9]. In this approach, the molecular groups attributed to the molecular mechanical (MM) subsystem are taken to be effective fragments that make electrostatic, polarization, and exchange contributions to the Hamiltonian of the quantum subsystem. The interactions between molecular groups (conformationally flexible effective fragments) attributed to the MM subsystem are described by classical force fields. To calculate the trajectories of particles in the MM subsystem, molecular dynamics, which describes motions of solids, is necessary. Previously [10], we described the first attempts to apply rigid-body molecular dynamics to a search for conformations with minimal energies using the replica-exchange algorithm. In the present paper, we report examples of calculations and analysis of trajectories with a new implementation of the QM/MD program.

To describe rigid body motion using explicit integration algorithms, two coordinate systems are introduced: the laboratory coordinate system $Oxyz$ and the body-fixed coordinate system $O'x'y'z'$ (Fig. 1). In the latter, the basis vectors are collinear with the principal axes of inertia of the body and the origin of the system O' coincides with the center of mass of a fragment [11]. The motion of a fragment, considered as a combination of a translation of the center of mass $\mathbf{q} = (q_x, q_y, q_z)$ with respect to $Oxyz$ and a rotation, is described by means of the vectors of the total momentum $\mathbf{p} = m\mathbf{v}_{com}$ determined with respect to the laboratory coordinate system and the angular momentum $\pi = \mathbf{I}\omega$ specified in the body-fixed coordinate system. Here, m and $\mathbf{v}_{com}$ are, respectively, the mass of the body and the velocity of the center of mass; $\mathbf{I}$ and ω are, respectively, the

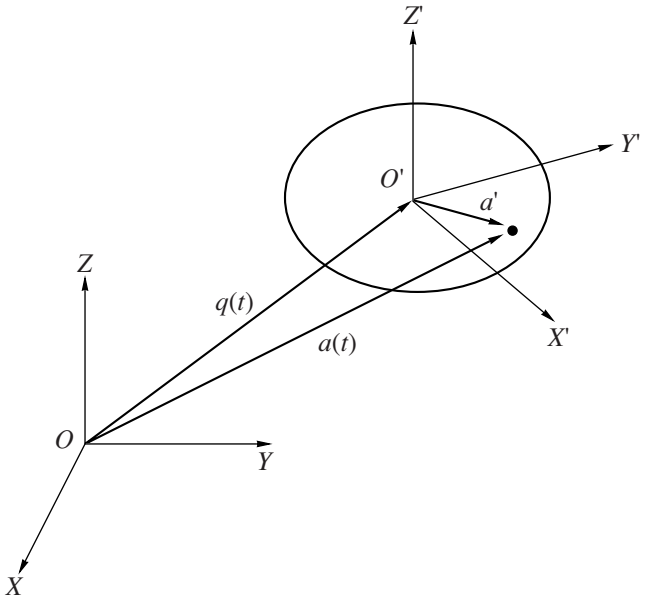

Fig. 1. Coordinate system in solid-body dynamics.

moment of inertia tensor and the angular velocity of the body. The interaction of a given fragment with the remaining part of the system is described by the overall force $\mathbf{f} = \sum_i \mathbf{f}_i$ acting on the body and by the overall moment of forces $\boldsymbol{\tau} = \sum_i \boldsymbol{\tau}_i$ calculated relative to the center of mass.

The dynamic equations describing the motion of the center of mass—$d\mathbf{p}/dt = \mathbf{f}$ and $d\mathbf{q}/dt = \mathbf{p}/m$—can be integrated either in the quaternion approximation [12] or by the rotation matrix method [13]. We chose the latter variant, in which the orientation of the fragment is specified by the matrix $\mathbf{Q}$ whose elements are the direction cosines between the laboratory coordinate system $Oxyz$ and the body-fixed coordinate system $O'x'y'z'$:

$$\mathbf{Q} = \begin{bmatrix} \cos(\mathbf{x} \wedge \mathbf{x}') & \cos(\mathbf{x} \wedge \mathbf{y}') & \cos(\mathbf{x} \wedge \mathbf{z}') \\ \cos(\mathbf{y} \wedge \mathbf{x}') & \cos(\mathbf{y} \wedge \mathbf{y}') & \cos(\mathbf{y} \wedge \mathbf{z}') \\ \cos(\mathbf{z} \wedge \mathbf{x}') & \cos(\mathbf{z} \wedge \mathbf{y}') & \cos(\mathbf{z} \wedge \mathbf{z}') \end{bmatrix},$$

where $\mathbf{a} \wedge \mathbf{b}$ is the angle between the vectors $\mathbf{a}$ and $\mathbf{b}$. In this case, the dynamic equation of the motion of the rigid fragment takes the form [13]

$$d\mathbf{p}/dt = \mathbf{f},$$

$$d\pi/dt = \tau + \pi(\mathbf{I}^{-1}\pi),$$

$$d\mathbf{q}/dt = \mathbf{p}/m,$$

$$d\mathbf{Q}/dt = \mathbf{Q}skew(\mathbf{I}^{-1}\pi),$$

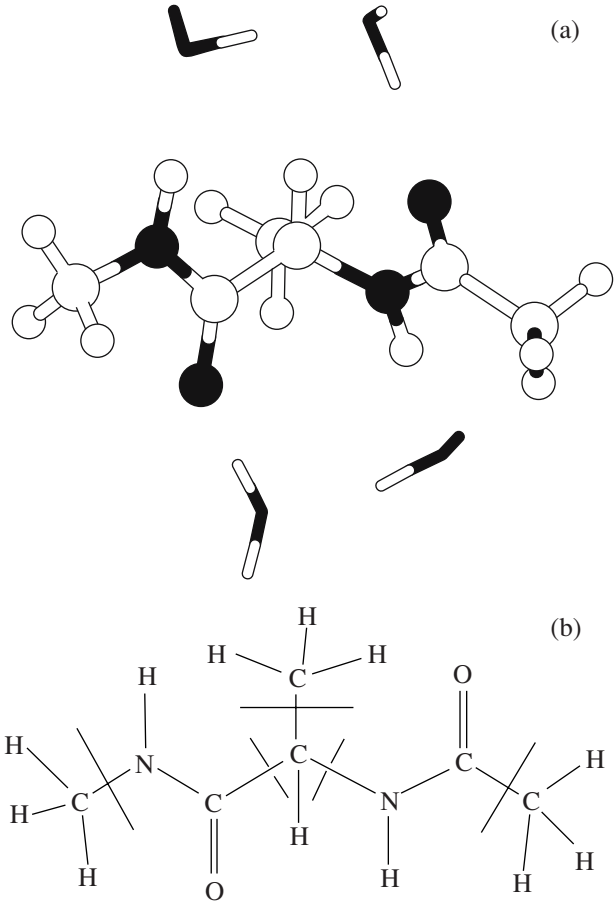

Fig. 2. (a) Model system consisting of the dipeptide *N*-acetyl-*L*-alanine-*N*'-methylamide and four water molecules and (b) partition of the dipeptide into effective fragments.

where $skew(\mathbf{a}) = \begin{bmatrix} 0 & -a_3 & a_2 \\ a_3 & 0 & -a_1 \\ -a_2 & a_1 & 0 \end{bmatrix}$.

We implemented a numerical algorithm that allows one to compute the MD trajectories in molecular systems partitioned into the QM domain and the MM domain represented by conformationally flexible chains of effective fragments moving as rigid bodies whose motion is described by the above equations. The energies and forces in the QM subsystem are calculated with the PC GAMESS program package [14].

The approach was first applied to a model system containing the dipeptide *N*-acetyl-*L*-alanine-*N*'-methylamide and four water molecules [5] (Fig. 2a). The water molecules were assigned to the QM part, and energies and forces were calculated at the Hartree–Fock level using the 6-31G basis set.

The dipeptide molecule was assigned to the MM subsystem, which is partitioned into six effective fragments (two CH_3, two CONH, and two CH fragments)

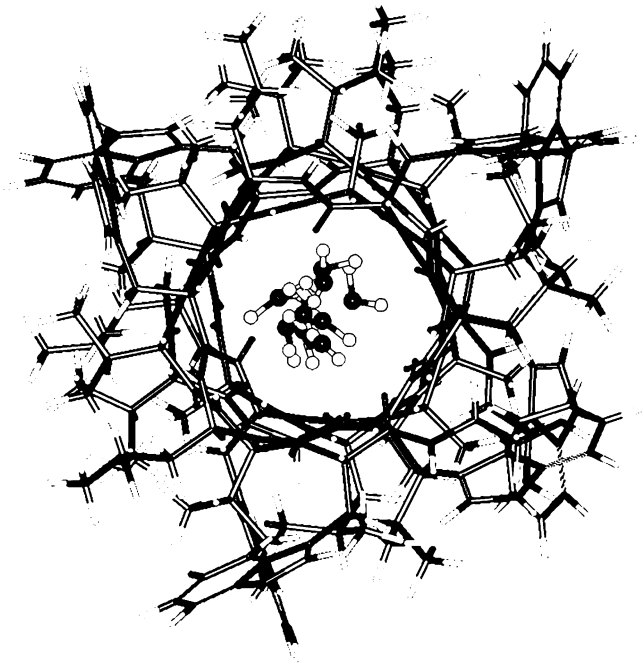

Fig. 3. Gramicidin dimer with the oriented chain of water molecules into the channel.

and is described by the OPLSAA force field parameters [15]. The integration of the QM/MD equations was performed in the NVE ensemble with an integration step of 0.5 fs and trajectory lengths of up to 3 ps. The calculations demonstrated satisfactory total energy conservation along all the trajectories.

In another example, we considered the movement of a proton along the oriented chain of water molecules inside the double helix of gramicidin constructed on the basis of the 1JNO structure from the protein structure database (Fig. 3). As the proton travels along the chain of water molecules, cleavages and formations of chemical bonds (inside a water molecule) and hydrogen bonds (between water molecules) occur. In calculations of trajectories, the water molecules and the extra proton were assigned to the QM subsystem described at the Hartree–Fock level with the 6-31G basis set. The molecular groups of gramicidin were partitioned into 144 effective fragments. The interaction between these fragments was described by the AMBER force field parameters [16]. At each point of the MD trajectory, each fragment of the MM subsystem contributes to the quantum Hamiltonian of the QM subsystem. The integration of the QM/MD equations was performed in the NVE ensemble with an integration step of 0.5 fs and trajectory lengths of up to 3 ps. All calculations were performed on common personal computers Pentium IV 3.03 GHz and Athlon XP 1800+. Quantum-chemical calculations need the largest CPU time. Our findings demonstrate the possibility of the practical implementation of a combined QM/MD method. We intend to further improve the procedure of applying molecular dynamics. Inasmuch as the major CPU time is consumed by calculations in the QM part of the system, the task of QM/MD simulation is rather untypical since, in most cases, the time consumed by calculation of the energy and force for a part of the system is proportional to the size of the subsystem. These specific features of the problem can be used for reducing the CPU time required by calculations. First of all, the following techniques can be used: (i) the use of the integration of equations of motion with a variable time step (for example, the Bulirsch–Stoer method [17]), (ii) approximation of the potential energy surface in those phase space regions where the trajectory has already passed, and (iii) distortion of the potential energy surface for the accelerated barrier crossing by the MD trajectory [18].

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