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Determination of molecular force field parameters for nitronyl nitroxide derivatives using quantum chemical calculations

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ABSTRACT

The molecular force field plays an important role in molecular design. The force field parameters of small molecules were obtained by applying quantum chemical calculations on a limited number of compounds. However, force field parameters for atypical compounds such as organic radicals have not been obtained yet. In this study, the energy profiles covering conformational changes of nitronyl nitroxide derivatives are calculated using quantum chemical calculations, and the force field parameters are obtained by curve fitting of the energy profiles. For calculating energy curves, we applied the hybrid density functional theory; the atomic charges of the test compounds were calculated based on the restricted electrostatic potential method. As the nitronyl nitroxide derivatives are considered to have great potential applications in biological sciences, the determined parameters are expected to be useful for the molecular design of organic radicals.

1. Introduction

Nitronyl nitroxide derivatives are stable organic radical compounds. Some nitronyl nitroxide derivatives are promising organic magnetic materials, such as the γ-phase crystal of 2-(4′-nitrophenyl)-4,4,5,5-tetramethyl-4 5-dihydro-1*H*–imidazol-1-oxy-3-*N*-oxide (*p*-NPNN) which is the initially found organic ferromagnet [1]. In nitronyl nitroxide derivative crystals, both intermolecular ferromagnetic interactions [1–3] and antiferromagnetic interactions [4–5] have been observed. In addition, the nitronyl nitroxide moiety can act as the ligand of transition metals, and the magnetic behavior of the complex has been observed [6]. In these cases, nitronyl nitroxides function as spin sources for molecular magnetic materials. However, as nitronyl nitroxide derivatives are stable organic radicals, not only their magnetic properties but also their biological activities are expected to be found in nitronyl nitroxide derivatives. For example, some papers reported the potential application of nitronyl nitroxides in antioxidant drugs, and chiral pyrrolyl α-nitronyl nitroxide [7], amino acid binding nitronyl nitroxides [8], and nitronyl nitroxide derivatives binding with peptide [9] were synthesized. The active oxygen species increase with aging; antiinflammatory, antiatherosclerotic, antitumor, antimutagenic, anticarcinogenic, antiparkinsonian, and anti-Alzheimer activities were found for the antioxidant compounds [10–13]. Pyrrolyl α-nitronyl nitroxide [7] was proposed as a candidate anti-Alzheimer drug because the compound decreased the deposition of amyloid β and tau phosphorylation in the mouse model and improved spatial learning and memory. Amino acid binding nitronyl nitroxide [8] decreased the oxidative stress and hepatic ischemia–reperfusion-induced injury in the rat model. In peptidic nitronyl nitroxide [9], not only free radical scavenging activity but also thrombolytic activity was observed. These observations suggest that stable organic radicals such as nitronyl nitroxide are promising drug candidate compounds.

Although nitronyl nitroxide derivatives play important roles not only in molecular magnetism but also in the development of biologically active compounds, computational methods for investigating nitronyl nitroxide for drug design and development have not been sufficiently prepared. Nowadays, costs for drug design continuously increase in terms of both money and time [14]. Thus, several compound properties such as efficacies, side effects, and toxicities are frequently predicted using computational procedures before experiments to reduce the number of actual experiments for compound syntheses and assays [15]. In computer-aided drug design (in silico drug design), various computational methods are used. Especially, classical mechanics are mainly used in in silico drug design because high-speed calculations for a large number of compounds are required for drug design. Classical molecular

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mechanics calculations and molecular dynamics simulations are used for investigating the behaviors of drug candidate compounds and biopolymers. In conformational search and in the evaluation of binding affinities between drugs and targets, classical mechanical energy functions are frequently used. Therefore, the force field parameters for calculating the energy of compounds are indispensable. However, these parameters were determined only for drug-like compounds, and the parameters for uncommon compounds were not sufficiently prepared. Although the parameters for ordinary organic compounds, amino acids, and nucleic acids were variously determined, the parameters for not-drug-like systems, such as transition metals and radicals, were not developed. As mentioned above, nitronyl nitroxide derivatives are stable organic radicals, which may be useful drug candidates. On the other hand, organic radicals were less considered in drug design and development trials, and their force field parameters were not prepared. Therefore, the force field parameters of nitronyl nitroxides have to be determined in order to use nitronyl nitroxide for in silico drug design.

Previously, we determined the molecular force field parameters of several moieties. The force field parameters of important groups for drug design research, such as the heme of cytochrome P450 [16] and the thioester moiety [17], have been developed. The accurate parameters were not prepared for these moieties in spite of their significance in drug design. Thus, we performed parameter fittings using energy profiles obtained by quantum chemical calculations. In this study, the force field parameters of nitronyl nitroxides are determined by similar procedures to these parameter fitting studies. We already conducted quantum chemical calculations of various nitronyl nitroxide derivatives, and their intermolecular magnetic interactions were successfully calculated [18–22]. These results indicate that the unrestricted hybrid density functional theory (DFT) calculations are appropriate for energy calculations of nitronyl nitroxide derivatives. In addition, we found that simplified models of nitronyl nitroxide derivatives can be used for quantum chemical calculations to evaluate the energy properties. These results suggest that the energy of nitronyl nitroxide can be divided into the energy terms of partial structures, and classical molecular mechanics methods can be used for nitronyl nitroxides. For applications to bioscience studies, we determine the classical molecular force field parameters of nitronyl nitroxides.

2. Methods

In this study, the force field parameters of nitronyl nitroxide derivatives were determined using the energy function of the AMBER force field [23–24], which is one of the most widely used molecular mechanical force field in biological researches. In the AMBER force field, the energy of the system is calculated by the energy function Eq. (1).

$$E_{\text{total}} = \sum_{\text{bonds}} \mathrm{K}_r(r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j}\left(\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right) \quad (1)$$

In this equation, the first and second terms, which are related to bond stretching and angle bending, respectively, express harmonic-oscillator approximations. The parameters r_{eq} and θ_{eq} are the equilibrium bond length and bond angle, respectively, and K_r and K_θ are force constants. The third term is the torsional term, where V_n is the energy barrier of torsional motion, n is the periodicity, and γ is the phase. The last term describes nonbonding interactions, van der Waals interactions, and Coulombic interactions. In this equation, r, θ, ϕ, and R_{ij} are the structural features of the system (bond length, bond angle, torsional angle, and the distance between atoms i and j, respectively). In the Coulombic term of nonbonding interactions, atomic charge approximation, in which the total charge is divided into partial charges assigned for all the atoms in the molecule, are used, and the electrostatic energies are calculated based on these atomic charges using the Coulomb equation. q_i and q_j are the atomic charges of atoms i and j, respectively. For the calculations of van der Waals interactions, 6–12 equation was used. The torsional term is the correction term for the nonbonding interactions. The residual portion of the energy that cannot be evaluated by Coulombic and van der Waals terms was corrected by the torsional term. In the AMBER force field, the parameters for amino acids and the nucleic acids were already determined. In addition, the parameters for drug-like small organic molecules were also defined, and these parameters were included in the generalized AMBER force field (GAFF) [25]. On the other hand, GAFF cannot be applied to nitronyl nitroxide derivatives because organic radicals are not considered drug-like compounds. Therefore, the force field parameters of nitronyl nitroxide derivatives were determined using both GAFF atom types and introduced atom types.

The compounds used for the parameter determinations of this study were the simplest nitronyl nitroxide derivative 4,4,5,5-tetramethylimidazolin-1-oxyl 3-oxide (HNN) and one of the simplest nitronyl nitroxide derivatives with the aromatic substitution of 2-position, 2-phenyl-4,4,5,5-tetramethylimidazolin-1-oxyl 3-oxide (PhNN). To these compounds, the new atom types were assigned for the important moiety for radical behavior, and the GAFF atom types were used for the rest. The molecular structures and the atom types in HNN and PhNN are illustrated in Fig. 1. For the atom types of hydrogens, "hc" and "ha" were used for the methyl hydrogens and the phenyl hydrogens, respectively. In the Fig. 1, the atom types "cn," "nn," and "on" were the new atom types for the carbon, nitrogen, and oxygen in the nitronyl nitroxide moiety. As mentioned above, atomic charges are frequently required for classical molecular force field calculations. In this study, the restricted electrostatic potential (RESP) charges [26], which are recommended for the AMBER calculations, were determined. To calculate RESP charges, electrostatic potentials obtained by quantum chemical calculations are required. We calculated the electrostatic potentials using the Hartree–Fock method with a 6-31G* basis set, which is recommended by the AMBER development team. However, unrestricted wave functions were used for the radical calculations.

The force field parameters were determined using the energy profiles of various conformations of the model compounds calculated by quantum chemical methods. The conformations were generated by changing the small portion of the model compound. For example, only one or two of r, θ, and ϕ were changed. In addition to quantum chemical energies, classical molecular mechanics energies, except for the undetermined parameter terms, were calculated by the "ready-made" force field. The difference between the quantum chemical energy and the classical "ready-made" energy was determined, and the parameter fitting using Eq. (1) for the energy difference was carried out. For the quantum chemical calculations, the unrestricted hybrid DFT method was used as described in previous studies [18–22]. In this study, the B3LYP exchange–correlation functional and the 6-31G** basis set were used. The quantum chemical calculations were performed using GAUSSIAN 09 [27]. Before the energy profile calculations, structural optimizations were conducted by UB3LYP/6-31G**. The classical molecular mechanics calculations were carried out by AMBER14 [24]. The GAFF force field was used as the "ready-made" force field.

As mentioned above, the three-dimensional structure of the small portion of the model compound was changed, and the energy