Difference in the Potential Energy Surfaces from the Fragment MO Method and Conventional Ab Initio SCF-MO Method. A Case of a Surface for Ring Rotation of (−)-Epicatechin Gallate Using the STO-3G Basis Set

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Difference in the potential energy surfaces (ΔE) obtained from the fragment MO (FMO) method and conventional ab initio Hartree–Fock SCF-MO (HFMO) method was investigated using the best fragmentation pattern of (−)-epicatechin gallate. In the lower energy region ($<$23.06 kcal mol^{-1} from the minimum), the average ΔE at each grid point was 1.1 kcal mol^{-1}. The FMO method is applicable to quantum MD calculation of large molecular system at around the standard temperature.

The fragment molecular orbital (FMO) method[1–4] has been proposed as a method to calculate the electronic structure for large molecular systems such as proteins and molecular clusters. In the FMO method, a target molecule is divided into small fragments, and the electronic structure for each fragment and fragment pair is calculated to obtain the total energy and other one-electron properties, such as dipole moment, of the entire molecule. Because the FMO method does not involve MO calculations on the whole molecule, computational cost of the FMO method is drastically reduced in comparison to that of the conventional MO method, especially for large molecules. Because MO calculations on each fragment and fragment pair in the FMO method can be performed independently, the FMO method is ideally suited for parallel processing.[2,4] Based on calculations on several polypeptides, using the ab initio Hartree–Fock SCF MO (HFMO) method as a reference,[2] the loss in accuracy when using the FMO method has been reported to be less than 1 kcal mol^{-1} for the total energy. Highly accurate FMO calculations for large molecules can be carried out on computer systems as small as a PC cluster, and are computationally inexpensive for evaluating the reactivities and chemical properties of large molecules.

In the FMO method, selection of the fragmentation position of a molecule and the distribution pattern of two electrons at a connecting bond is crucial for achieving highly accurate electronic structure calculations. The accuracy of the FMO method has only been confirmed for fragmentation at a sp^3 C–C bond, especially the Cα–C* bond of a protein and enzyme[4] and the C4′–C5′ bond of deoxyribose in DNA, because applications of the FMO method have focused mainly on proteins and DNA. The accuracy of the FMO method must still be confirmed for fragmentation of large molecular systems in general, such as autacoids and polymers. We have reported some important results on the minimum energy structure of (−)-epicatechin gallate ((−)-ECg).[5] Some of them are as follows: Both the total energy difference and atomic charge difference between the FMO and HFMO methods are quite sensitive to the fragmentation pattern. A "best" pattern exists for individual molecules, for which results comparable to HFMO calculations can be achieved. For highly accurate FMO calculations, the number of electrons for each fragment should be close to neutral, and the electrons in the fragmentation bond should be redistributed to a sp^3 carbon in the case of C–C bond.

It is known that extension and bending of a fragmented bond gives a very small difference ($<$0.1 kcal mol^{-1}) in the total energy.[6] In this study, difference in two dimensional potential energy surfaces (ΔE) for ring rotation of (−)-ECg (Fig. 1) calculated from the FMO and HFMO methods were evaluated to confirm the applicability of the FMO method for quantum molecular dynamics (QMD) simulation. (−)-ECg is a type of tea catechin, and is known as an autacoid for physiologically active substances that undergoes anti-oxidative reactions in biosystems. First, for the best fragmentation pattern of (−)-ECg (Fig. 1), ΔE was evaluated at grids on the potential energy surface consisting of χ_1 and χ_2. There are three fragments in the pattern. χ_1 is rotation at a bond in a fragment, and χ_2 is a rotation at a connecting bond.

Average of ΔE on each grids was 1.1 kcal mol^{-1} at the lower energy region where the energy was up to 23.06 kcal mol^{-1} (=1.16 × 10^4 K) from the minimum. It is suggested that the

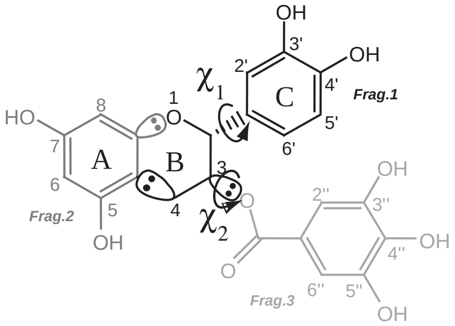

Fig. 1. Molecular geometry, pattern of bonding-electron distribution and positions of rotation axis (χ_1 and χ_2) of (−)-ECg.

FMO method using a “best” fragmentation pattern is applicable to QMD at ≈300 K.

Calculation

ABINIT-MP Ver.20021029[2,4,7] was used for the FMO calculation, and Gaussian98W Rev.-A.7[8] was used for the HFMO calculation. The threshold for the SCF convergence (1.0×10^{-8} and 1.0×10^{-6} in energy and the maximum difference of diagonal elements in density matrix, respectively) and accuracy of molecular integrals (1.0×10^{-12}) were the same for both calculations. All calculations were performed using the STO-3G basis set. (−)-ECg has 52 atoms, 230 electrons, and 180 basis functions. Starting with χ_1 and χ_2 at the minimum geometry being 0.0, 144 (12×12) grids were generated by changing χ_1 and χ_2 from 0.0 to 360.0° in steps of 30.0°. The geometrical parameters except for χ_1 and χ_2 on each grid were fixed to the parameters of the minimum energy structure.

All calculations using the FMO and HFMO methods were performed on a notebook PC, IBM ThinkPad T41, which had Microsoft Windows XP, a Pentium M 1.6 GHz processor, 1 GB of memory and 40 GB hard disk drive.

Result and Discussion

Potential energy surfaces (PES) of the HFMO are depicted in Fig. 2. PES of the FMO was almost the same as that in Fig. 2. Difference in the PESs from the HFMO and the FMO was hard to see on this scale. Two peaks, which were higher than 4000 kcal mol^{-1}, at $(\chi_1, \chi_2) = (30.0, 120.0)$ and (210.0, 120.0) in both cases.

A wall, which was higher than 900 kcal mol^{-1}, was observed at about $\chi_2 = 180.0$ in Fig. 2. Difference in the PES (ΔE) between the HFMO and FMO methods is shown in Fig. 4. Two walls were almost 860 kcal mol^{-1} high and 280 kcal mol^{-1} at around $\chi_2 = 180.0$ and 240.0, respectively.

Because χ_1 seems to be independent in Fig. 3, the potential energy and ΔE at $\chi_1 = 0.0$ are shown in the upper and lower figures in Fig. 4. In the upper figure, open circles are the energies from the HFMO method, and filled circles are from the FMO method. Using the FMO method three peaks, denoted **A**, **B**, and **C**, could be reproduced. ΔE at peak **A** was small, but ΔEs at peaks **B** and **C** were very large.

Figures 5, 6, and 7 show molecular conformations at the peaks **A**, **B**, and **C**, respectively. In the molecular conformation at the peak **A**, the keto oxygen of gallate was very close to C1′ and C2′ of ring C, but ΔE was small because C1′ and C2′ of ring C were not atoms at a junction. The keto oxygen was however close to O1 of ring B in the conformation at peak **B**. O1 of ring B was a junction atom connecting two fragments. In the conformation at peak **C**, the keto oxygen was close to C10 of ring A. C10 of ring A was a junction atom connecting two fragments. Thus, in the high-energy region, ΔE becomes very large when an atom is close to junction atoms connecting two fragments.

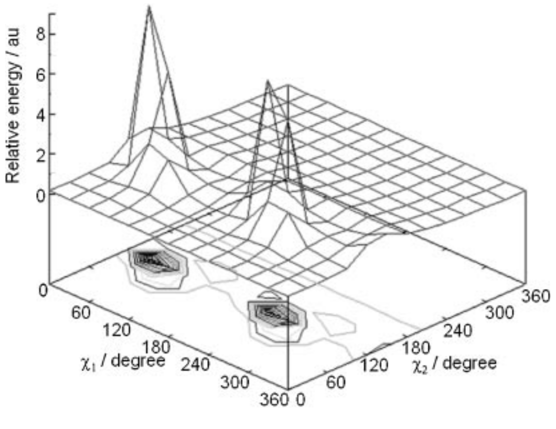

Fig. 2. Potential energy surface by the HFMO method.

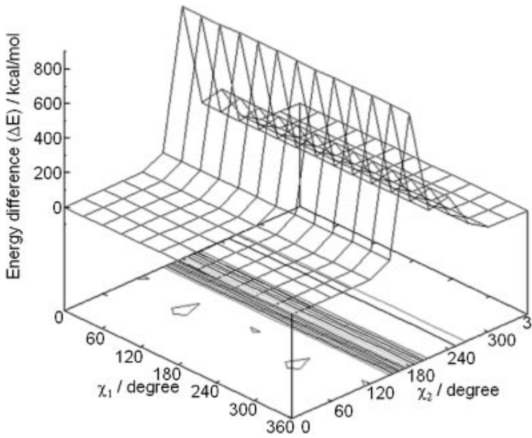

Fig. 3. Difference of the potential energy surfaces (ΔE) between the HFMO and FMO methods.

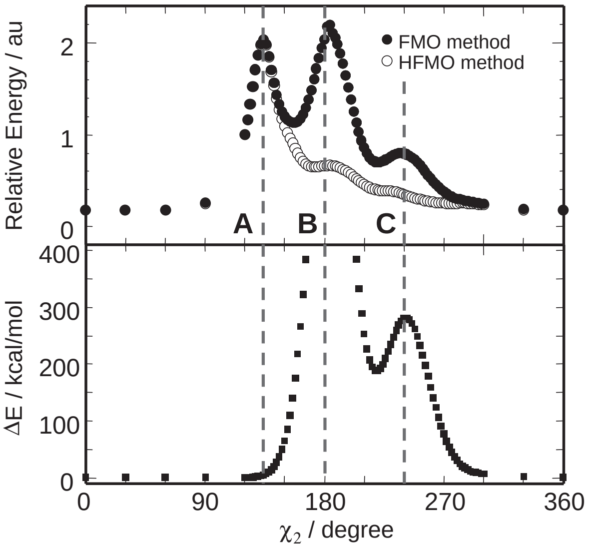

Fig. 4. Potential energy (au) and ΔE (kcal mol^{-1}) at $\chi_1 = 0.0$. Upper is the potential energy surfaces of the HFMO method (open circles) and the FMO method (filled circles).

These peaks and wall were, however, too high for usual MD simulations at around standard temperatures. In usual MD simulation, the temperature is lower than 10000 K (nearly equal to 20 kcal mol^{-1}). We, therefore, focused our discussion on the lower-energy region, where the potential energy is lower than 1.0 eV.

Figure 8 shows ΔE in the region $-30.0 < \chi_2 < 60.0$ where the potential energy is lower than 1 eV (=23.06

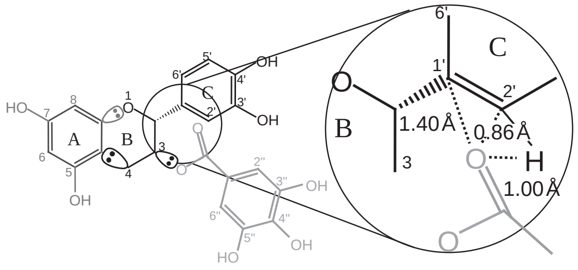

Fig. 5. Molecular conformation at the peak **A**.

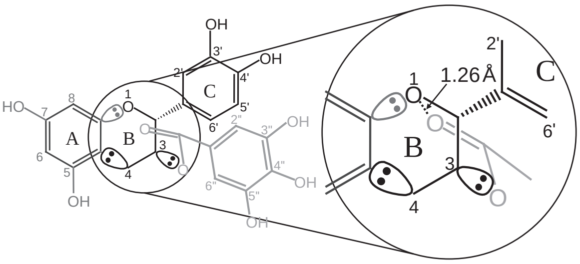

Fig. 6. Molecular conformation at the peak **B**.

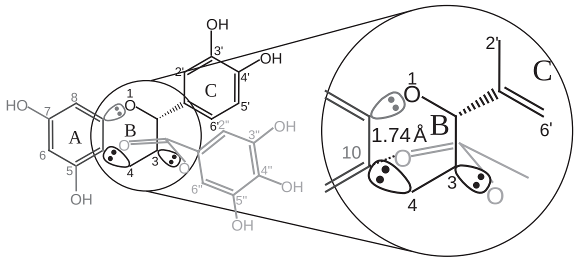

Fig. 7. Molecular conformation at the peak **C**.

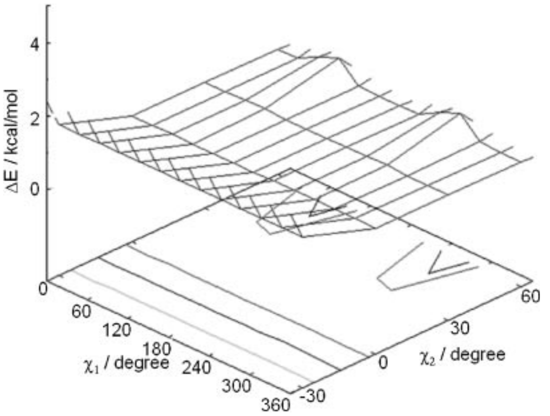

Fig. 8. ΔE in the region $-30.0 < \chi_2 < 60.0$ where the potential energy is lower than 1 eV ($=23.06\,\mathrm{kcal\,mol^{-1}} = 1.16 \times 10^4\,\mathrm{K}$).

$\mathrm{kcal\,mol^{-1}} = 1.16 \times 10^4\,\mathrm{K}$). This energy region is usually sufficient for MD simulation of a biomolecule. The position that has maximum ΔE ($=2.2\,\mathrm{kcal\,mol^{-1}}$) was at $\chi_2 = -30.0$, because this position is already close to peak **C**. The averaged values of ΔE and its standard deviation in the region were $1.1\,\mathrm{kcal\,mol^{-1}}$ and 0.28, respectively. This strongly suggests that the FMO method is applicable to quantum MD calculation of large molecular system at standard temperatures.

Conclusion

Difference in two dimensional PES (ΔE) for ring rotation of (−)-ECg from the FMO and HFMO methods were evaluated to confirm applicability of the FMO method for quantum molecular dynamics (QMD) simulation. First, for the best fragmentation pattern of (−)-ECg, ΔE was evaluated at grids on the PES consisted of χ_1 and χ_2. In the high-energy region, ΔE is very large when an atom is close to atoms located at a bond that is fragmented.

On the other hand, the average ΔE of each grids was $1.1\,\mathrm{kcal\,mol^{-1}}$ in the lower-energy region, where the energy was up to $23.06\,\mathrm{kcal\,mol^{-1}}$ ($=1.16 \times 10^4\,\mathrm{K}$) from the minimum. This suggests that the FMO method using a "best" fragmentation pattern is applicable to QMD at $\approx$300 K. Thus, the accuracy of the PES should be carefully evaluated if MD sampling using FMO method is carried out at high temperatures ($>$10000 K).

Though inter and intra relaxations of fragment are excluded in this study, inclusion of the relaxations of fragments seems to cause the extension of low-potential region. It means that actual region where the FMO works well is wider than that shown in this study.

Unfortunately, discussion about the quality of the basis set and ΔE are not given in this study. Though the basis set STO-3G is insufficient to describe weak interaction in biosystems, a large sample number is possible, because of light computational cost. The analysis of ΔE with different basis set is in progress.

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