Bull. Chem. Soc. Jpn. Vol. 81, No. 1, 110–112 (2008)

Ab Initio MO-MD Simulation Based on the Fragment MO Method. A Case of (−)-Epicatechin Gallate with STO-3G Basis Set

Katsuhiro Tamura,[1,2] **Toshio Watanabe,**[3,4] **Takayoshi Ishimoto,**[3,4] **and Umpei Nagashima***[1,3,4]

[1]Department of Chemistry, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8571

[2]Shizuoka Industrial Research Institute of Shizuoka Prefecture, 2078 Makigaya, Aoi-ku, Shizuoka 421-1298

[3]Research Institute for Computational Sciences, National Institute of Advanced Industrial Science and Technology, 1-1-1 Umezono, Tsukuba 305-8568

[4]Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, 4-1-8 Honcho, Kawaguchi 332-0012

Received May 29, 2007; E-mail: u.nagashima@aist.go.jp

We performed ab initio MO-MD simulation based on the fragment MO (FMO) method using the (−)-epicatechin gallate in order to examine the efficiency of fragmentation pattern in comparison with conventional MO-MD. We clearly demonstrated that the FMO-MD simulation gave sufficient results concerning the trajectory of the total energy and the geometry difference.

The function of a biological molecule, such as a protein, depends on its folded structure, stability, physical properties, and dynamics, i.e., conformational fluctuations.[1] To analyze the folding process, conformational fluctuations, and their relation to protein functions, it is necessary to elucidate the dynamics of the biological molecules.

Due to the rapid progress in the development of computational techniques and new methodologies for treating large molecules, ab initio calculations of large molecules are now possible. The fragment molecular orbital (FMO) method[2–6] has been proposed by Kitaura and co-workers for calculating large molecules such as proteins and molecular clusters. The FMO method divides a large molecule into fragments and calculates the MOs of fragments and fragment pairs to obtain the total energy and other properties of the whole molecule. Applications of the FMO method to biological molecules have been reported,[7] and the range of applications of FMO method including geometry optimization is being continually expanded.[8,9] Furthermore, it is expected that the molecular dynamics (MD) simulation based on FMO method will enable us to explore the origin and function of biological molecules. Recently, we have developed the FMO-Hamiltonian algorithm (FMO-HA) method, which is one technique within the ab initio MO-MD method.[10,11] The FMO-MD method is expected to determine the driving force for conformational fluctuations in biological molecules by analyzing the changes in intermolecular and intramolecular interaction energies between fragments that occur during dynamics simulation.

In the FMO method, selection of the fragmentation position of a molecule and distribution pattern of two electrons at a breaking 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 and the C4′–C5′ bond of deoxyribose in DNA, because applications of the FMO method have mainly focused on proteins and DNA. We have reported the fragmentation pattern dependence of the total energy and atomic charge difference of (−)-epicatechin gallate ((−)-ECg).[12] We have found that a "best" pattern exists for individual molecules, for which results comparable to HFMO calculations can be achieved. Also, the difference (ΔE) in the potential energy surfaces (PES) between the FMO method and conventional ab initio MO method have been investigated using the best fragmentation pattern of (−)-ECg.[13] In our previous paper,[13] we have reported that the average of ΔE at each grid point is 1.1 kcal mol^{-1} in the lower energy region (<23.06 kcal mol^{-1} from minimum). It is expected that the FMO method is applicable to quantum MD calculations using the best fragmentation pattern.

In this study, we performed FMO-HA dynamics simulation using the best fragmentation pattern of (−)-ECg in order to examine the efficiency of fragmentation pattern in comparison with conventional MO-MD calculation. We also analyzed another fragmentation patterns of (−)-ECg for a comparison with the best fragmentation pattern.

Computational Method

The initial geometry of the (−)-ECg was determined at the RHF/STO-3G level[14] using the Gaussian 03 program package.[15] Figure 1 shows the molecular structure of (−)-ECg. We selected 3 fragment patterns for (−)-ECg calculation (see Fig. 2), because these fragmentation patterns accurately represented the total energy and electronic population obtained by conventional MO. In order to perform the ab initio MO-MD calculation, the FMO-HA method was applied to the (−)-ECg, also at the RHF/STO-3G level, because the computational cost of the FMO-HA calculation with large basis set is very expensive at this time.

In our HA-based approach, we considered the virtual motion

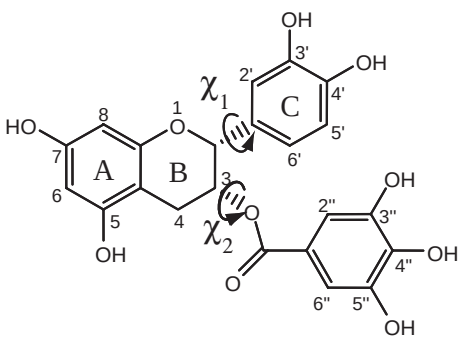

Fig. 1. Molecular structure of (−)-ECg.

Published on the web January 10, 2008; doi:10.1246/bcsj.81.110

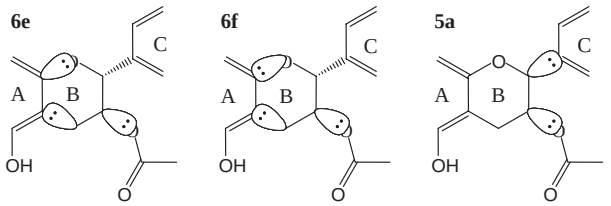

Fig. 2. Molecular fragmentation patterns and bonding-electron distribution.

of the atomic nuclei x of the cost function $V(x)$, which is the energy value calculated by the FMO method. The Hamiltonian of the motion of each atom has following form:

$$H(p,x) = \frac{1}{2}\sum_{i,j}\frac{b_{ij}p_ip_j}{\sqrt{m_im_j}} + V(x), \quad (1)$$

where p_i and p_j are momentums, and m_i and m_j are masses of atomic nuclei i and j, respectively. The first term of the right-hand side of the equation is the virtual kinetic energy of the whole molecule. The off-diagonal term shows the mixing of the motions of each atomic nucleus, and the coefficient b_{ij} is a positive definite symmetric matrix that represents the degree of mixing. This mixing procedure provides an effective search of the energy surface.[16] When the off-diagonal terms are zero, FMO-HA is equivalent to ab initio FMO-MD simulation. In this study, we focused on the analysis of the efficiency of FMO-MD simulation as a first step, although the HA-based approach is expected to do an effective search of the energy surface as an ab initio MD simulation for large molecules.

FMO-HA simulations were performed for 2000 steps for (−)-ECg, with a time step of 1.0 fs. We have already found the efficiency of the PES obtained by the FMO method in the lower energy region. To be able to search global space in a short time, the high kinetic energy (KE), 0.1 a.u., was assigned as the initial conditions for (−)-ECg. We used 0.0 as the mixing coefficient in order to perform conventional FMO-MD simulation with constant number of particles, volume, and energy (NVE) ensemble (called "microcanonical ensemble"). All FMO-MD calculations were performed with the modified FMO method program ABINIT-MP.[17]

Results and Discussion

We focused on the two dihedral angles χ_1 and χ_2, in Fig. 1 in order to analyze the efficiency of FMO-MD method. The χ_1 and χ_2 obtained by using the stable structure of (−)-ECg were 87.9 and 141.2 degrees, respectively. We converted χ_1 and χ_2 to 0.0 as a criterion in this study. From the difference in PES between conventional MO and FMO shown in Fig. 8 of Ref. 13, the energy difference is small, and the shape of PES is shallow in the region of χ_1 (0.0–360 degrees) and χ_2 (−30–60 degrees). The trajectory of χ_1 and χ_2 during the MO-MD simulation of (−)-ECg with initial KE = 0.1 a.u. is shown in Fig. 3**A**. The trajectory of χ_1 and χ_2 by the MO-MD simulation was traced from −40 to 40 degrees and from −30 to 20 degrees, respectively. This result clearly shows good agreement with the PES in Ref. 13 The trajectory of χ_1 and χ_2 during the FMO-MD simulation of (−)-ECg is also shown in Fig. 3. The trajectory in Fig. 3**B** is the case of fragmentation pattern **6e**. The fragmentation pattern **6e** was used to analyze the difference of PES in Fig. 8 of Ref. 13. The conformational search on χ_1 and χ_2 obtained by FMO-MD simulation are fully represented the MO-MD result, because the trajectory of χ_1 and χ_2 obtained by the FMO-MD simulation traced the same region (from −40 to 40 degrees and from −30 to 20 degrees of χ_1 and χ_2, respectively) as that obtained by the MO-MD in a short time.

In addition, we analyzed the difference in the fragmentation patterns. The fragmentation pattern **6f** has same quality as the

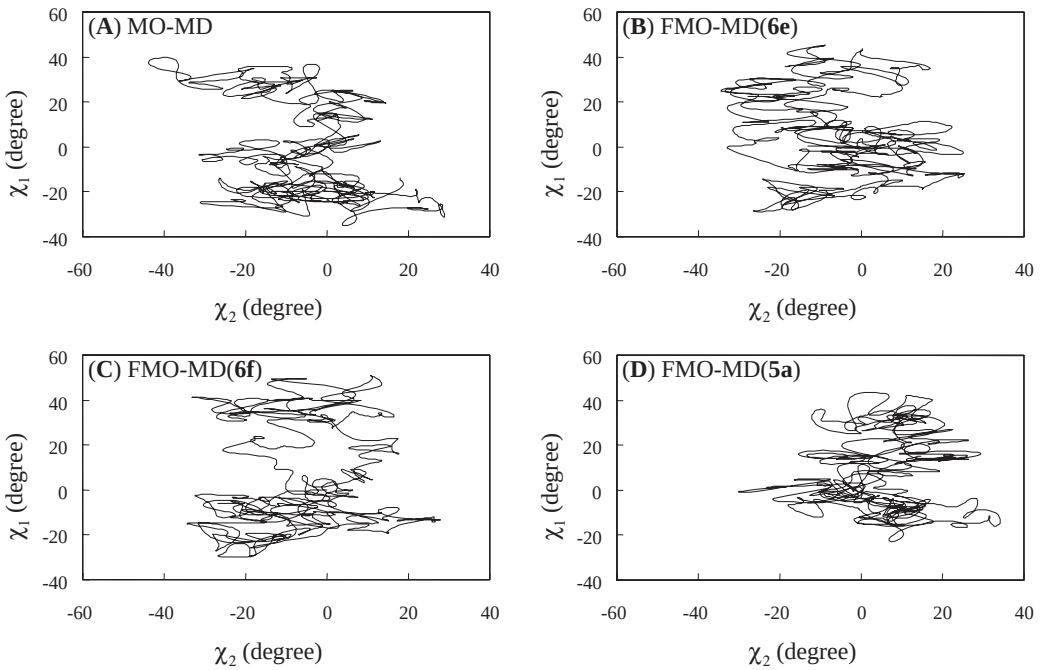

Fig. 3. The trajectory of χ_1 and χ_2 during dynamics simulation of (−)-ECg. The MO-MD is shown in (**A**). The FMO-MD with fragmentation patterns **6e**, **6f**, and **5a** are shown in (**B**), (**C**), and (**D**), respectively.

Table 1. RMSΔE (kcal mol^{-1}), RMS$\Delta\chi_1$, RMS$\Delta\chi_2$, $\Delta\chi_1$, and $\Delta\chi_2$ (degree) between MO-MD and FMO-MD during the Simulation with Max. (+) and Max. (−) (degree) of χ_1 and χ_2

		(−)-ECg	6e	6f	5a
RMSΔE[a]			2.92	3.44	3.09
χ_1	Max. (+)[b]	39.7	45.2	51.0	43.5
	Max. (−)[c]	−34.9	−28.9	−30.0	−22.9
	RMS$\Delta\chi_1$[a]		1.7	2.5	2.7
	$\Delta\chi_1$[d]		18.8	19.5	23.6
χ_2	Max. (+)[b]	28.9	25.3	27.8	34.2
	Max. (−)[c]	−43.9	−34.5	−34.4	−30.2
	RMS$\Delta\chi_2$[a]		0.2	0.8	1.6
	$\Delta\chi_2$[d]		15.4	13.3	13.2

a) Root mean square error. b) Maximum positive deviation. c) Maximum negative deviation. d) Standard deviation.

6e. The trajectory of fragmentation pattern **6f** shown in Fig. 3**C** gives a similar conformational search so that using MO-MD and FMO-MD for **6e**. The same simulation was performed for fragmentation pattern **5a**, which is about 1.0 kcal mol^{-1} higher in total energy than **6e**. Although the conformational search was localized around the positive site of χ_2, we have found same tendency as that using MO-MD.

We next analyzed the detailed geometry changes with total energy of during the FMO-MD simulation. Table 1 summarizes the root mean square (RMS) of ΔE between MO-MD and FMO-MD during the simulation. We also show the maximum positive deviation (Max. (+)) and maximum negative deviation (Max. (−)) of χ_1 and χ_2 together with RMS$\Delta\chi_1$ and RMS$\Delta\chi_2$. The RMSΔE is only 1–2 kcal mol^{-1} higher than the difference between MO and FMO calculations. The Max. (+) and Max. (−) of χ_1 and χ_2 in FMO-MD are similar to those from MO-MD. RMS$\Delta\chi_1$ and RMS$\Delta\chi_2$ are very small. In order to analyze the efficiency of the PES obtained by the FMO-MD calculation, the values of standard deviation of χ_1 and χ_2 are also shown in the Table 1. Because the values of standard deviation of χ_1 and χ_2 for all fragmentation patterns were about 14.0 and 20.0, respectively, this result suggests that the shapes of PES of **6e**, **6f**, and **5e** obtained by FMO-MD are almost the same as each other. We clearly showed that the FMO-MD simulation is sufficient for determining the total energy and geometry differences.

Conclusion

In this work, we performed the FMO-MD dynamics simulation using the best fragmentation pattern of (−)-ECg in order to examine the efficiency of fragmentation pattern in comparison with conventional ab initio MO-MD calculation. The conformational search on χ_1 and χ_2 obtained by FMO-MD simulation are the same as that from the conventional MO-MD method. We showed that the FMO-MD simulation can be used to determine the trajectory of total energy and geometry difference. We also analyzed another fragmentation pattern of (−)-ECg for the comparison with best fragmentation pattern. These results confirm the efficiency of the FMO-MD simulation using various fragmentation patterns which accurately described the total energy.

This work was supported by the research project, "Development of MO calculation system for large molecule on Grid." CREST, Japan Science and Technology Agency.

References

1 M. Ferrand, A. J. Dianoux, W. Petry, G. Zaccai, *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 9668.
2 K. Kitaura, E. Ikeo, T. Asada, T. Nakano, M. Uebayasi, *Chem. Phys. Lett.* **1999**, *313*, 701.
3 T. Nakano, T. Kaminuma, T. Sato, Y. Akiyama, M. Uebayasi, K. Kitaura, *Chem. Phys. Lett.* **2000**, *318*, 614.
4 K. Kitaura, S. Sugiki, T. Nakano, Y. Komeiji, M. Uebayasi, *Chem. Phys. Lett.* **2001**, *336*, 163.
5 T. Nakano, T. Kaminuma, T. Sato, K. Fukuzawa, Y. Akiyama, M. Uebayasi, K. Kitaura, *Chem. Phys. Lett.* **2002**, *351*, 475.
6 D. G. Fedorov, K. Kitaura, *J. Chem. Phys.* **2004**, *120*, 6832.
7 K. Fukuzawa, Y. Mochizuki, S. Tanaka, K. Kitaura, T. Nakano, *J. Phys. Chem. B* **2006**, *110*, 16102.
8 D. G. Fedorov, K. Kitaura, *J. Chem. Phys.* **2004**, *121*, 2483.
9 D. G. Fedorov, K. Kitaura, *J. Chem. Phys.* **2005**, *122*, 054108.
10 T. Ishimoto, H. Tokiwa, H. Teramae, U. Nagashima, *Chem. Phys. Lett.* **2004**, *387*, 460.
11 T. Ishimoto, H. Tokiwa, H. Teramae, U. Nagashima, *J. Chem. Phys.* **2005**, *122*, 094905.
12 K. Tamura, Y. Inadomi, U. Nagashima, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 721.
13 K. Tamura, T. Watanabe, T. Ishimoto, U. Nagashima, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1939.
14 W. J. Hehre, R. F. Stewart, J. A. Pople, *J. Chem. Phys.* **1969**, *51*, 2657.
15 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian 03, Revision B.05, Gaussian, Inc., Pittsburgh PA, **2003**.
16 K. Ohtawara, H. Teramae, *Chem. Phys. Lett.* **2004**, *390*, 84.
17 ABINIT-MP, NIHS, available from http://moldb.nihs.go.jp/abinitmp.