Ab initio computations for the ring-opening potential of propylene oxide: roles of a proton and a water molecule

Hiroyuki Shinoda,[1,*] Michio Sayama,[2] Yoshihiro Mori,[1] and Mineyuki Mizuguchi[1]

[1] Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan

[2] Faculty of Engineering, Toyama University, Gofuku 3190, Toyama 930-8555, Japan

Abstract

Ab initio computations for the ring-opening potential of propylene oxide were carried out. The calculations of MP2/6-31G**, MP2/6-31++G**, MP3/6-31G**, MP3/6-31++G**, and QCISD/6-31G** were used to obtain the most stable structure of propylene oxide. The MP2/6-31G** method was used to calculate the ring-opening potentials for five systems, an isolated propylene oxide, a hydrated propylene oxide, a protonated propylene oxide, a protonated and hydrated propylene oxide, and a propylene oxide with a hydronium ion. Adding a proton was found to lower the potential barrier of the ring-opening reaction. It was found from the results of the localized molecular orbitals that the oxygen atom of a water molecule approaching the carbon atom of a C-O bond binds to the carbon atom to complement the insufficiency of the valence of the carbon atom. Furthermore, we carried out calculations for the ring-opening reaction of a protonated propylene oxide using MP2/6-31++G**, MP3/6-31G**, MP3/6-31++G**, and MP4SDQ/6-31G** methods. Our results suggest that the ring-opening process of a protonated propylene oxide is a one-step process.

Keywords. Ab initio computation, ring-opening reaction, propylene oxide, localized MO.

1 INTRODUCTION

The carcinogenic and/or mutagenic properties of vinyl compounds and of aromatic compounds have been investigated by many researchers. In particular, the chlorinated compounds have become well-known as strong carcinogens [1-12]. Henschler and Neudecker [1] investigated variations in the mutagenic properties of chloropropenes with respect to the number of substituted chlorine atoms and to the substituted positions. In their experiments, they used three enzyme inhibitors to trace the activated metabolic intermediates in the metabolic processes and found two metabolic pathways. One is the epoxidative pathway, in which an oxide is produced as an essential intermediate. Another is the hydrolytic-oxidative pathway, in which an aldehyde is produced as an essential intermediate. Although oxides are usually converted to diols by hydrolysis, Henschler and Neudecker concluded from their results that chloropropene oxides are converted to chloropropanals and not diols. In this case, oxides must be converted to propanals via both a ring-opening reaction and a hydrogen transfer reaction.

The ring-opening reactions of ethylene oxide and propylene oxide have been investigated by both experimental and quantum chemical computational methods [13-19]. Based on the results of thermal gas-phase decomposition and of single-pulse shock tube, it has been reported that an activation energy of 58.5 kcal/mol is needed for the ring-opening reaction of propylene oxide

[13,14]. In an acidic solution, the activation energy decreases to 18.62 kcal/mol [15]. For protonated ethylene oxide, the energy is 20 kcal/mol [16]. In computational research, similar results have been obtained [17-19]. As shown in Chart 1, the oxide-to-aldehyde conversion process must include both a ring-opening reaction and a hydrogen transfer reaction. The computed results for propylene oxide indicate that both reactions proceed in concert [17]. On the other hand, it was shown that for a protonated propylene oxide, the conversion to an aldehyde proceeds in a two-step reaction [18]. Duuren has described the carcinogenic action of vinyl chloride [20], indicating that there is a spontaneous rearrangement of monochloroethylene oxide to monochloroacetaldehyde. We have therefore had an interest in finding a spontaneous ring-opening process for propylene oxide.

Chart I
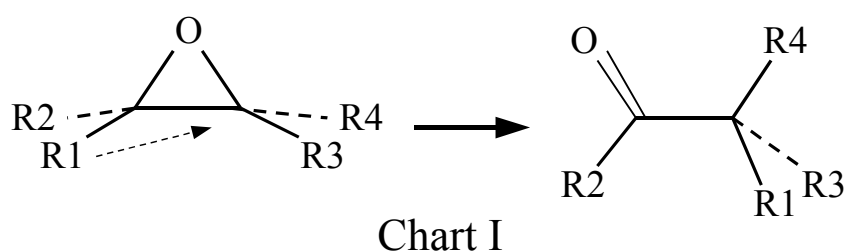
In the present study we investigated five systems, an isolated propylene oxide (**1**), a hydrated propylene oxide (**2**), a protonated propylene oxide (**3**), a protonated and hydrated propylene oxide (**4**), and a propylene oxide with a hydronium ion (**5**), by quantum chemical calculations using the MP2/6-31G** level. Furthermore, localized molecular orbitals were calculated for systems **1**, **3**, and **4**. The influences of basis sets and electronic correlations to the ring-opening reaction were also investigated for some systems.

2 Methods of calculation

All calculations were performed using the Gaussian98 program [21] installed on an SGI-Origin-3400 computer of Toyama Medical and Pharmaceutical University. The optimizations of **1** ~ **5** were carried out using the MP2/6-31G** level of calculations. In addition, optimizations of **1** were performed using MP2/6-31++G**, MP3/6-31G**, MP3/6-31++G**, and QCISD/6-31G** levels. The ring-opening potentials of **1** ~ **5** were calculated using the MP2/6-31G** level. Localized molecular orbitals have been obtained by the Boys' method in Gaussian98. The ring-opening potential of **3** was obtained using MP2/6-31++G**, MP3/6-31G**, MP3/6-31++G**, MP4SDQ/6-31G** levels.
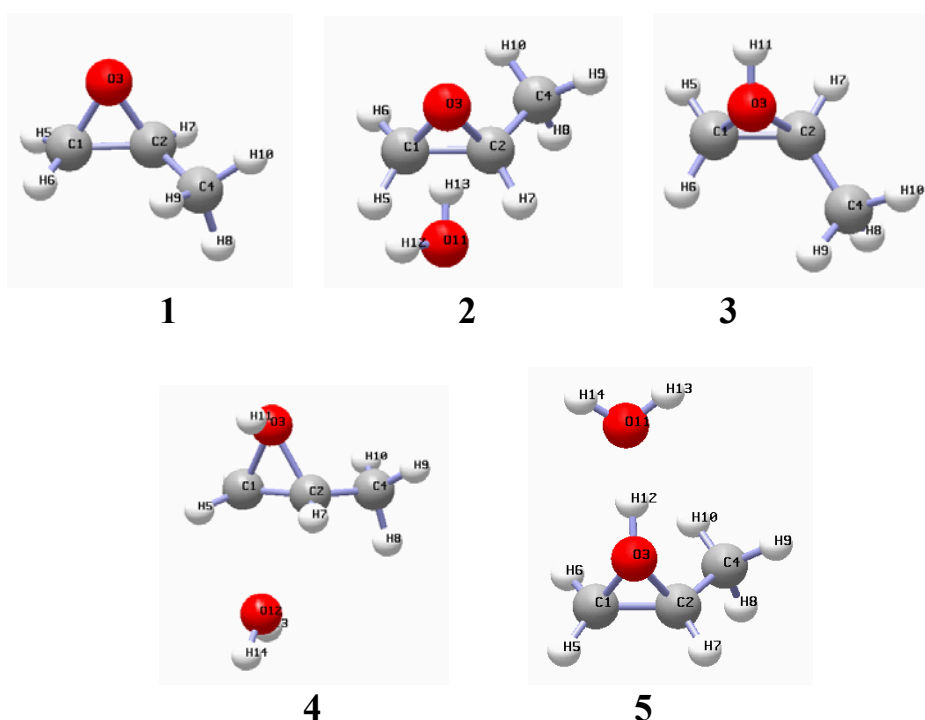
Figure 1. Stable structures of **1** ~ **5** calculated by the MP2/6-31G** method and the numbering of atoms.

1: an isolated propylene oxide, **2**: a hydrated propylene oxide, **3**: a protonated propylene oxide, **4**: a protonated and hydrated propylene oxide, **5**: a propylene oxide with a hydronium ion.

3 RESULTS AND DISCUSSION

3.1 Optimized Structures and Charge Densities of Propylene Oxides

The optimized structures of **1** ~ **5** by the method of the MP2/6-31G** level are shown in Fig. 1. The numbering of atoms in each compound is also shown in the figure, and the heavy atoms at the same positions in **1** ~ **5** have been assigned the same values. Although in the initial geometry of **5** a hydronium ion was placed close to the epoxide oxygen atom, the optimized structure in the figure has been found to be like a water molecule binding to the hydrogen atom of **3**. The optimized geometrical parameters of the oxide ring are listed in Table 1. The results in the table reveal that the lengths of the C-O bonds in neutral and cationic compounds differ from each other. The lengths of the C-O bonds in **1** and **2** were found to be 1.44 ~ 1.45 Å, while they were 1.52 ~ 1.57 Å in **3** and **4**. The lengths of the C-O bonds in **5** were found to be between these values. It was found in common through **1** ~ **5** that the length of a C-O bond involving a carbon atom binding to a methyl residue is greater than that of another C-O bond in the same compound. On the other hand, variations in the lengths of the C_2-C_4 bonds in **1** ~ **5** show the opposite tendency to those of the C-O bonds. That is,

the lengths of the C_2-C_4 bonds in neutral compounds of **1** and **2** are longer than those in protonated compounds of **3**, **4** and **5**.

Table 1. The main geometrical parameters of propyrene oxide.

	1	2	3	4	5
bonds (Å)					
C_1-C_2	1.4648	1.4631	1.4611	1.4485	1.4610
C_1-O_3	1.4413	1.4516	1.5206	1.5443	1.4980
C_2-O_3	1.4411	1.4530	1.5613	1.5699	1.5223
C_2-C_4	1.5006	1.4990	1.4860	1.4847	1.4930
angles (°)					
C_1-C_2-O_3	59.46	59.71	60.30	61.39	60.24
C_2-C_1-O_3	59.45	59.80	63.12	63.18	61.91
C_1-C_2-C_4	121.81	122.02	123.18	122.9	122.75

Table 2. Total atomic charges of heavy atoms in propylene oxide by Mulliken's population analysis for optimized structures of **1** ~ **5(5')** and atomic charges with hydrogens. (au)

	1	2	3	4	5(5')
Total atomic charges					
C_1	-0.0251	-0.0381	-0.0389	-0.0029	-0.0484(-0.0484)
C_2	0.1103	0.0975	0.0592	0.0896	0.0835(0.0826)
O_3	-0.4681	-0.4906	-0.3886	-0.4161	-0.4594(-0.4556)
C_4	-0.3482	-0.3477	-0.3708	-0.3698	-0.3940(-0.3931)
Atomic charges with hydrogens					
C_1	0.2137	0.2301	0.4512	0.4588	0.3928(0.3939)
C_2	0.2316	0.2508	0.2966	0.3123	0.3136(0.3038)
O_3	-0.4681	-0.4906	0.0389	0.0013	0.0240(0.0283)
C_4	0.0228	0.0334	0.2135	0.1882	0.1437(0.1434)

The atomic charges obtained from Mulliken's population analysis are listed in Table 2. These results indicate that only C_2 carbon in each compound has a positive charge, while other heavy atoms have a negative charge. It can be inferred from the electrostatic interactions that the C_1-O_3 bond is weaker than the C_2-O_3 bond. Dubnikova and Lifshitz [17] have performed DFT calculations of propylene oxide and have shown that the activation energy of a C_1-O_3 rupture producing a propanone is lower than that of a C_2-O_3 rupture producing a propanal. Flowers [13] has measured the products from the gas phase decomposition of propylene oxide, determining the activation energies needed to produce propanone and propanal. These results show that the

activation energy to produce propanone is larger than that to produce propanal. Lifshitz and Tamburu [14] have come to a similar conclusion based on experiments using a single-pulse shock tube. Long and Lifshitz [22] have used mass spectrometry to measure the hydrolysis products from propylene oxide and isobutylene oxide, finding that the C-O bond ruptures in a neutral solution show the same tendencies as those just described above. In an acidic solution, however, it was found that a C_2-O_3 bond is broken more easily than a C_1-O_3 bond. In Table 2 the atomic charges with hydrogens summed into heavy atoms are shown. It was found that the atomic charge of an epoxide oxygen atom depends on the total molecular charge. In the neutral systems of **1** and **2**, the oxygen charge is negative, while in the cationic systems of **3,4**, and **5**, it is positive. The atomic charges with hydrogens for carbon atoms are all positive. These results imply that ruptures of the C-O bond in protonated systems occur more easily than those in neutral systems.

Table 3. Dependency of the geometrical parameters and charge densities in **1** on the calculating methods.

	MP2		MP3		QCISD
	6-31G**	6-31++G**	6-31G**	6-31++G**	6-31G**
bond lengths (Å)					
C_1-C_2	1.4648	1.4666	1.4679	1.4697	1.4677
C_1-O_3	1.4413	1.4484	1.4308	1.4346	1.4368
C_2-O_3	1.4411	1.4474	1.4298	1.4328	1.4357
C_2-C_4	1.5006	1.5007	1.5042	1.5046	1.5055
Total atomic charge (au)					
C_1	-0.0251	-0.0421	-0.0063	-0.0101	-0.0022
C_2	0.1103	0.0489	0.1198	0.0684	0.1211
O_3	-0.4681	-0.3841	-0.4899	-0.3958	-0.4873
C_4	-0.3482	-0.4115	-0.3325	-0.3912	-0.3231
Atomic charges with hydrogens (au)					
C_1	0.2137	0.1986	0.2256	0.2083	0.2248
C_2	0.2316	0.1843	0.2382	0.1912	0.2370
O_3	-0.4681	-0.3841	-0.4899	-0.3958	-0.4873
C_4	0.0228	0.0012	0.0261	-0.0037	0.0254

In order to investigate the influences of basis sets and electronic correlations on geometrical parameters and atomic charges, we carried out calculations for **1** using the methods of MP2/6-31++G**, MP3/6-31G**, MP3/6-31++G**, and QCISD/6-31G** levels. The results obtained from the calculations are listed in Table 3. The differences of bond lengths between several methods are small in comparison with the differences between the several systems in Table 1. For examples, the

difference in C_2-O_3 bond lengths in Table 1 is 0.1288 Å, while that in Table 3 is 0.0176 Å. In the case of atomic charges with hydrogens, a similar tendency is shown in the results of Tables 2 and 3. Regarding the usual atomic charges, however, we found no identifiable trend. These results suggeste that sophisticated calculations are not needed to qualitatively investigate the structures and atomic charges.
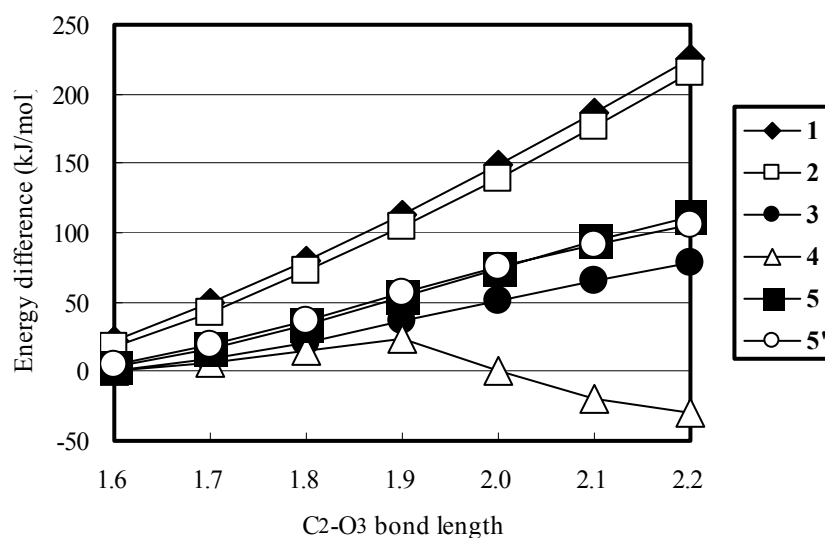

Figure 2. The ring-opening potential variations with respect to C_2-O_3 bond length (Å) of **1** ~ **5** and **5'**.

3.2 Ring-opening Potentials

Figure 2 shows the ring-opening potential variations with respect to the C_2-O_3 bond lengths of epoxide for **1** ~ **5** and **5'**. **5'** means the SCRF calculations of **5**. A lowering of energy was only at the C_2-O_3 distance of 2.2 Å in **4**. In no other cases shown in this figure was a lowering of energy observed. The increases in the potential energies of **4** and **5** (**5'**) with increases in the C_2-O_3 bond lengths are less steep than those of **1** and **2**. It can also be seen that the potential curves of **5** and **5'** are slightly different from each other, suggesting that using the reaction fields in calculating the ring-opening potentials does not bring about meaningful changes in the potentials. Therefore **5'** is excluded from consideration in all of the discussion below. The variations in the potential energies in **1** ~ **5** are consistent with the data in Table 2. That is, from the perspective of electrostatic interactions, the C_2-O_3 bonds in cationic systems are weaker than those in neutral systems.
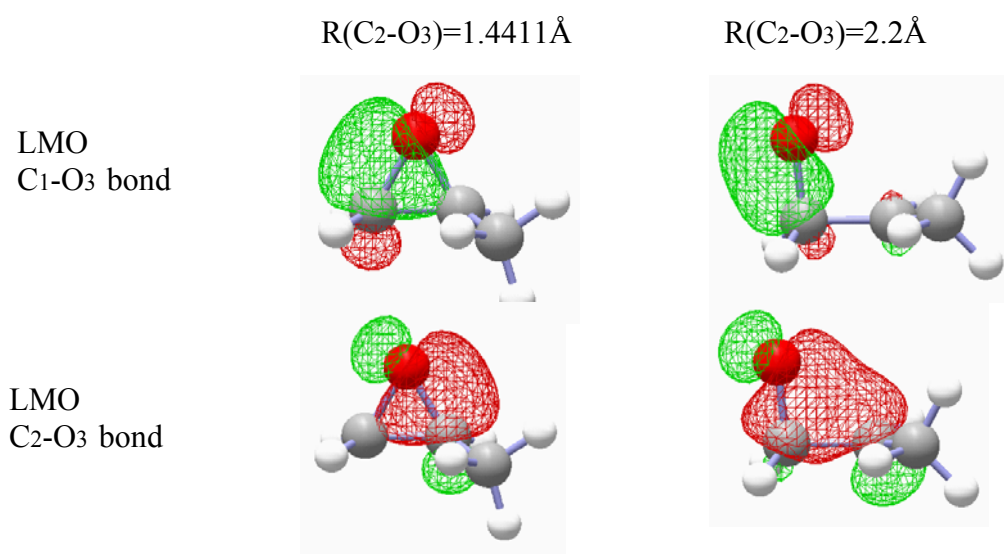
R(C$_2$-O$_3$)=1.4411Å   R(C$_2$-O$_3$)=2.2Å

LMO
C$_1$-O$_3$ bond

LMO
C$_2$-O$_3$ bond

Figure 3. The localized molecular orbitals (LMOs) on C$_1$-O$_3$ and C$_2$-O$_3$ bonds
of **1** at lengths 1.4411 and 2.2 Å of the C$_2$-O$_3$ bond.

R(C$_2$-O$_3$)=1.5613Å   R(C$_2$-O$_3$)=2.2Å

LMO
C$_1$-O$_3$ bond
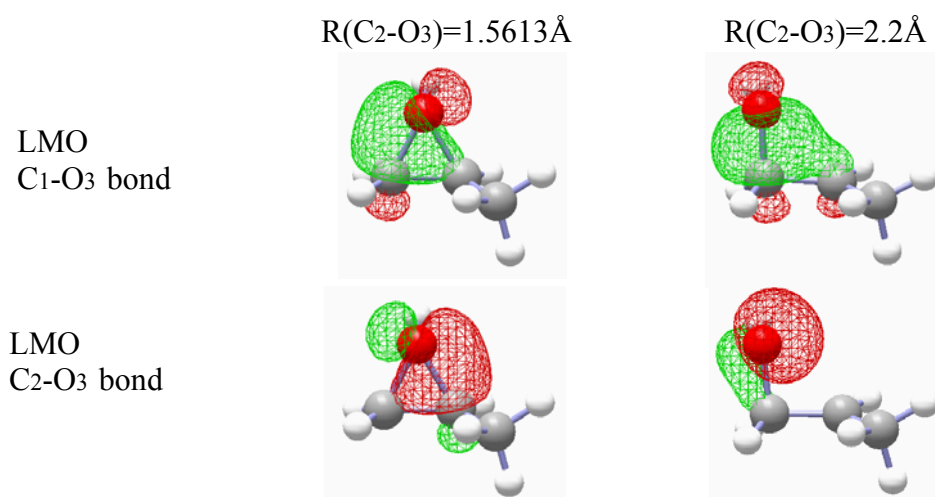
LMO
C$_2$-O$_3$ bond

Figure 4. The localized molecular orbitals (LMOs) on C$_1$-O$_3$ and C$_2$-O$_3$ bonds
of **3** at lengths 1.5613 and 2.2 Å of the C$_2$-O$_3$ bond.

Three **3**, **4**, and **5** systems are protonated cationic cases. Only **4** among them demonstrated a decrease in potential energy at a C$_2$-O$_3$ bond length of 2.2 Å. To identify differences between **3** and **4** and between neutral and acidic solutions, localized molecular orbital calculations were carried out for **1**, **3**, and **4**. The localized molecular orbitals (LMOs) related to C$_1$-O$_3$ and C$_2$-O$_3$ bonds for **1**, **3**, and **4** are shown in Figures 3, 4, and 5, respectively.
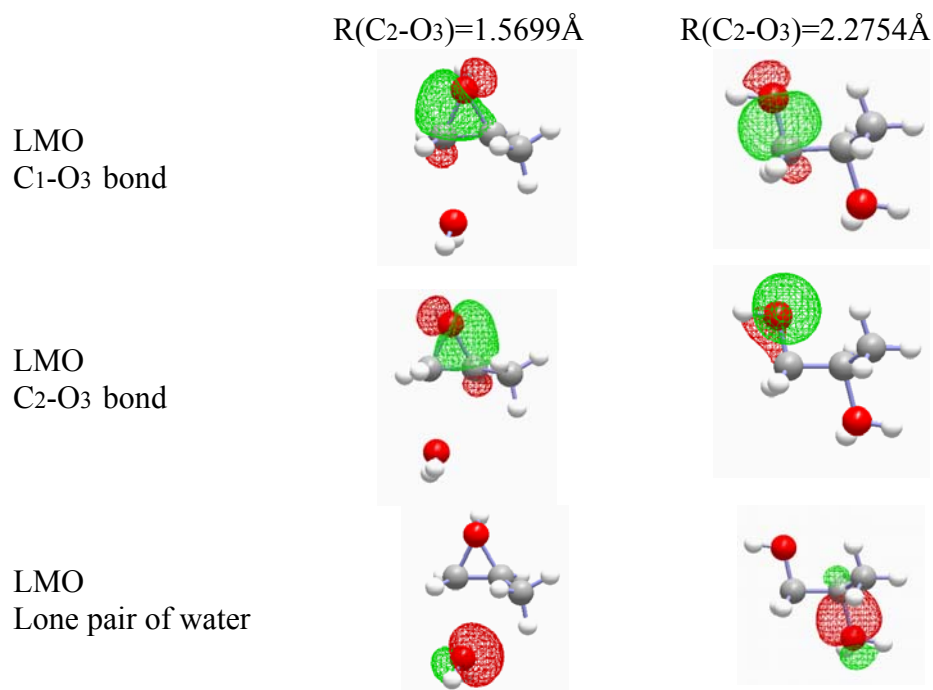
Figure 5. The localized molecular orbitals (LMOs) on C_1-O_3 bond, C_2-O_3 bond, and lone pair prbital of water of **4** at lengths 1.5699 and 2.2754 Å of the C_2-O_3 bond.

In Fig. 5, furthermore, a lone pair orbital of the oxygen atom in a water molecule is also shown. LMO localized on a C_1-O_3 bond is expected to be invariable through cleavage of the C_2-O_3 bond. On the other hand, the LMO on the C_2-O_3 bond is expected to transform to a lone pair orbital of the oxygen atom through this cleavage. It can be seen in Fig. 3 that even when the C_2-O_3 bond length is 2.2 Å, the LMO on the C_2-O_3 bond never transforms to a lone pair orbital. In contrast, in Fig. 4 it is shown that the LMO localized on a C_2-O_3 bond does become the lone pair orbital of an oxygen atom. It can also be seen in the figure that the LMO localized on the C_1-O_3 bond expands into a C_2 atom when the C_2-O_3 bond length is 2.2 Å. In each case there is one LMO that resists the C_2-O_3 bond cleavage which makes cationic cite of C2 atom and brings the atom an unsatisfactory valence. It is shown from Fig. 5 that when the length of the C_2-O_3 bond is 2.2754 Å, the LMO on the C_2-O_3 bond is transformed into a lone pair orbital of an oxygen atom. It is also shown that the LMO on the C_1-O_3 bond is scarcely expanded to a C_2 atom. One important situation in Fig. 5 is the conversion of a lone pair orbital of the oxygen atom in the water molecule to a new bond to a C_2 carbon atom when the C_2-O_3 bond is 2.2754 Å. The LMOs in **4** when the C_2-O_3 bond length is 2.2754 Å have forms almost identical to the LMOs when the length is 2.2 Å. The C_2-O_3 bond length is 2.2754 Å for the fully optimized structure obtained from the calculation starting with the initial structure of

2.2 Å. The results of the LMO calculations indicate that the unsatisfactory valence of the C_2 atom resists rupture of the C_2-O_3 bond. It also appears that the existence of a nucleophilic reagent complementing the valence accelerates the ring-opening reaction.
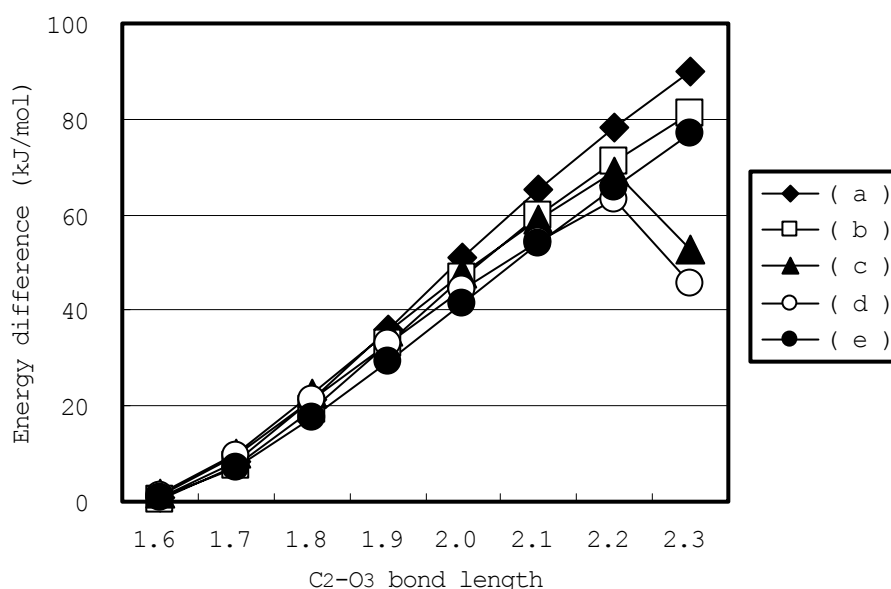

Figure 6. The ring-opening potential variations with respect to C_2-O_3 bond length (Å) of **3**.
(a) MP2/6-31G**, (b) MP2/6-31++G**, (c) MP3/6-31G**, (d) MP3/6-31++G**,
(e) MP4SDQ/6-31G**.

One of our interests is the reaction path of making propanal through the ring-opening of a propylene oxide. In order to complete the process of producing a propanal from a propylene oxide, one of the hydrogen atoms binding to a C_1 atom of propylene oxide must transfer to a C_2 atom. Dubnikova and Lifshitz [17] have concluded that both the ring-opening process of propylene oxide and the hydrogen transfer process proceed via concerted mechanisms in neutral gas phase conditions. Coxon *et al.* [18], however, have concluded that in protonated propylene oxide, two processes occur in different steps. In our results, a stable structure with a 2.2 Å C_2-O_3 bond was found only in **4**. In this case, a water molecule binds the C_2 atom. As such, the transfer of a hydrogen atom from the C_1 atom to the C_2 atom may not be preferred over the approach of a water molecule to the C_2 atom. In the case of **3**, we performed more sophisticated computations, utilizing MP2/6-31++G**, MP3/6-31G**, MP3/6-31++G**, and MP4SDQ/6-31G** methods. The results

regarding the ring-opening potentials are shown in Fig. 6 along with the MP2/6-31G** result from Fig. 2. When the C_2-O_3 bond length is 2.3 Å, a decrease in potential energies can be seen in two methods. A common point in the two cases is the MP3 level of the electronic correlation. Full optimization calculations were performed from the initial structures, which were obtained by partial optimization, fixing the C_2-O_3 length to 2.3 Å. The results of the calculation using the MP3/6-31G** method indicate that a hydrogen transfer from the C_1 atom to the C_2 atom occurs, and that there is a 0.01 au decrease in the quantity of the potential energy from propylene oxide. The results of the calculation using the MP3/6-31++G** method, however, indicate that there is no hydrogen transfer and that the structure and the potential energy change slightly changed from those of 2.3 Å. If no calculations in this study could give a hydrogen-transfer structure, it could be said that the ring-opening process of propylene oxide proceeds without a hydrogen transfer occurring in a concerted manner. However, there is one case where a hydrogen-transfer structure was obtained; therefore it must be suggested that the process of obtaining propanal from propylene oxide is a one-step reaction. Quantitative analysis involving an exact transition structure and IRC calculations will be carried out in the near future.

4 CONCLUDING REMARKS

Quantum chemical calculations were performed for five systems: an isolated propylene oxide, a hydrated propylene oxide, a protonated propylene oxide, a protonated and hydrated propylene oxide, and a propylene oxide with a hydronium ion. The aim of these calculations was to reveal what conditions allow spontaneous completion of the ring-opening process of propylene oxide to create a propanal. Two conclusions can be drawn from our results. The first is that the ring-opening process never proceeds spontaneously under any conditions, even in acidic conditions. The second is that both the ring-opening process and the hydrogen transfer process appear to proceed in a one-step process.

5 REFERENCES

[1]   T. Neudecker and D. Henschler, Mutagenicity of chloroolefins in the salmonella/mammalian microsome test III, *Mutation Res*. **1986**, *170*, 1-9.
[2]   C. Drevon and T. Kuroki, Mutagenicity of vinyl chloride, vunylidine chloride and chloroprene in V79 chinese hamster cells, *Mutation Res*. **1979**, *67*, 173-182.
[3]   M. M. Shahin and R. C. von Brostel, Mutagenic and lethal effects of α-benzene hexachloride, dibutyl phthalate and trichloroethylene in saccharomyces cerevisiae, *Mutation Res*. **1977**, *48*, 183-190.
[4]   W. Kanhai, W. Dekant, and D. Henschler, Metabolism of the nephrotoxin dichloroacetylene by glutathione conjugation, *Chem. Res. Toxicol*. **1989**, *2*, 51-56.
[5]   B. L. Van Duuren, B. M. Goldschmidt, G. Loewengart, A. C. Smith, S. Melchlonne, I. Seidman, and D. Roth, Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice, *J. Natl. Cancer Inst*. **1979**, *63*, 1433-1439.

[6]   M. Lag, J. G. Omichinski, E. Dybing, S. D. Nelson, and E. J. Soderlund, Mutagenic activity of halogenated propanes and propenes: effect of bromine and chlorine positioning, *Chemico-Biol. Inter.* **1994**, *93*, 73-84.

[7]   K. Hagen and R. Stolevik, Conformational energies and structures of chloropropenes, *J. Mol. Struct.* **1996**, *376*, 83-102.

[8]   P. Kolandaivel and N. Jayakumar, Structure and conformational stability of CH_2CHCH_2X (X=F, Cl and Br) molecules — post Hartree-Fock and density functional theory methods, *J. Mol. Struct. (Theochem)* **2000**, *507*, 197-206.

[9]   B. J. van der Veken and W. A. Herrebout, Conformational Stability from Temperature-Dependent FT-IR Spectra of Liquid Rare Gas Solutions, Barriers To Internal Rotation, Vibrational Assignment, and Ab Initio Calculations for 3-Chloropropene, *J. Phys. Chem.* **A 1999**, *103*, 6142-6150.

[10] P. R. Laurence, T. R. Proctor, and P. Politzer, Reactive Properties of trans-Dichlorooxirane in Relation to the Constrasting Carcinogenicities of Vinyl Chloride and trans-Dichloroethylene, *Int. J. Quantum Chem.* **1984**, *26*, 425-438.

[11] J. S. Murray and P. Politzer, A Computational Study of Some Isomerization Equilibria and Their Possible Relation to Vinyl Chloride Carcinogenicity, *Int. J. Quantum Chem.* **1987**, *31*, 569-579.

[12] E. Eder, T. Neudecker, D. Lutz, and D. Henschler, Mutagenic potential of allyl and allylic compounds, *Biochem. Pharmac.* **1980**, *29*, 993-998.

[13] M. C. Flowers, Kinetics of the Themal Gas-Phase Decomposition of 1,2-Epoxypropane, *J. Chem. Soc., Faraday Trans.* **1977**, *73*, 1927-

[14] A. Lifshitz and C. Tamburu, Isomerization and Decomposition of Propylene Oxide. Studies with a Single-Pulse Shock Tube, *J. Phys. Chem.* **1994**, *98*, 1161-1170.

[15] F. A. Long, J. G. Pritchard, and F. E. Stafford, Entropies of Activation and Mechanism for the Acid-catalyzed Hydrolysis of Ethlene Oxide and its Derivatives, *J. Am. Chem. Soc.* **1957**, *79*, 2362-2364.

[16] R. D. Bowen, D. H. Williams, and G. Hvistendahl, Potential Surfaces for the Unimolecular Reactions of Organic Ions: $C_2H_6N^+$ and $C_2H_5O^+$, *J. Am. Chem. Soc.* **1977**, *99*, 7509-7515.

[17] F. Dubnikova and A, Lifshitz, Isomerization of Propylene Oxide. Quantum Chemical Calculations and Kinetic Modeling, *J. Phys. Chem.* **A 2000**, *104*, 4489-4496.

[18] J. M. Coxon, R. G. A. R. Maclagan, A. Rauk, A. J. Thorpe, and D. Whalen, Rearrangement of Protonated Propene Oxide to Protonated Propanal, *J. Am. Chem. Soc.* **1997**, *119*, 4712-4718.

[19] G. P. Ford and C. T. Smith, Gas-Phase Hydrolysis of Protonated Oxirane. Ab Initio and Semiempirical Molecular Orbital Calculations, *J. Am. Chem. Soc.* **1987**, *109*, 1325-1331.

[20] B. L. Van Duuren, On the possible mechanism of carcinogenic action of vinyl chloride, *Ann. N. Y. Acad. Sci.* **1975**, *246*, 258-267.

[21] Gaussian 98, Revision A.9, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratman, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. A. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, 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, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.

[22] F. A. Long and J. G. Pritchard, Hydrolysis of Substituted Ethylene Oxides in H_2O Solutions, *J. Am. Chem. Soc.* **1956**, *78*, 2663-2667.

Biographies

Hiroyuki Shinoda is research associate of Structural Biology at the Faculty of Pharmaceutical Science, Toyama Medical and Pharmaceutical University (Japan). After obtaining the PH.D degree in physical chemistry from Waseda University, Dr. Shinoda investigated IR and Raman intensities by theoretical calculations. Hs research interest is in differences of chemical properties of biological substances between in gas-phase and in aqueous-phase.

Michio Sayama is assistant professor of the department of material systems engineering and life science, Faculty of engineering, Toyama University (Japan). After obtaining the Ph.D degree in Toyama Medical and Pharmaceutical University, Dr. Sayama undertook postdoctoral research at Maryland University (USA). Recently, Dr. Sayama engages himself in research of metabolic activation of carcinogen. His research area spreads from analytical science and quantum chemistry to biochemistry and molecular biology. Sayama's interest is the fusion of vital phenomenon and quantum chemistry.

Yoshihiro Mori is research associate at the Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University)Japan). He obtained the Ph.D degree in physical chemistry from University of Tokyo. Dr. Mori has investigated the reactivity of molecules solubilized in a small water or organic cluster with several

experimental methods such as mass spectroscopy combined with a supersonic molecular beam technology and laser-induced transient absorption spectroscopy. Recently, Dr. Mori has a great interest in electric percolation phenomena occurred via fusion of small water droplets in a reversed micellar solution.

Mineyuki Mizuguchi received his Ph.D. degree in molecular biology from the Graduate School of Science, Hokkaido University, Japan, and carried out postdoctoral studies on protein folding at the Scripps Research Institute, USA. He is presently Associate Professor of Pharmaceutical Sciences at the Toyama Medical and Pharmaceutical University, Japan. His research interest includes the protein structure and misfolding associated with amyloid diseases.