http://dx.doi.org/10.5012/bkcs.2011.32.9.3465

Notes

Theoretical Studies on the Photocyclization of *o*-ethoxybenzophenone and *o*-2,2,2-trifluoroethoxybenzophenone

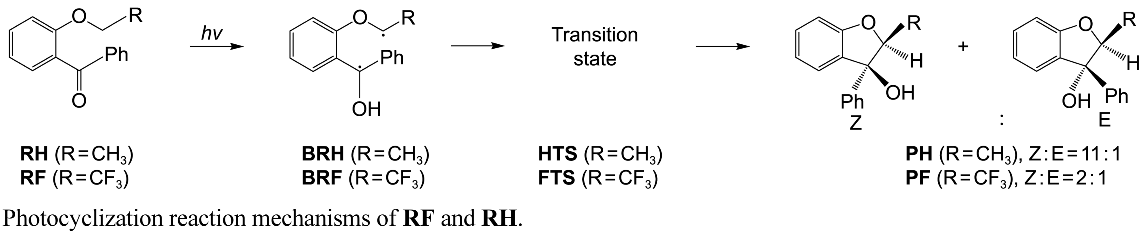
Jiho Park[†] **and Hahkjoon Kim**[*]

Department of Chemistry, Duksung Women's University, Seoul 132-714, Korea. [*]*E-mail: khj730516@ds.ac.kr*
[†]*Department of Environmental Health , Korea National Open University, Seoul 110-791, Korea*

Received March 26, 2011, Accepted April 26, 2011

Key Words : Biradical, Photocyclization, Diastereoselectivity, Density functional theory

Biradical intermediates, produced *via* Norrish type II reaction, play an important role in many chemical reactions.[1,2] Owing to its high reactivity, some aromatic biradicals produced *in vivo* are known to cleave double stranded DNA by abstracting a hydrogen atom from each DNA strand.[3] It is well-known that substituent groups attached to radical centers greatly influence the branching ratio of the final products.[4,5] Especially, a disubstituted carbon radical displays enhanced stability when an electron acceptor group and an electron donor group are attached to a carbon centered radical as compared to two electron acceptor groups or electron donor groups are attached on a carbon centered radical.[6] When a biradical intermediate is prostereogenic, diastereoselectivity can be created in the course of cyclization by the rotation of a single bond.[7,8] In the field of organic chemistry, diastereoselective synthesis is important because the reactions of synthetic drugs with biomolecules are often stereoselective.[9,10] As shown in Figure 1, Park and Kim have reported that *o*-ethoxybenzophenone (**RH**) undergoes a photochemical reaction in benzene *via* intramolecular hydrogen migration followed by cyclization to produce dihydrobenzofuranol (**PH**) with a Z/E ratio of 11:1 in benzene, whereas *o*-2,2,2-trifluoroethoxybenzophenone (**RF**) produces 2-trifluoromethyl-3-phenyldihydrobenzofuran-3-ol (**PF**) with a Z/E ratio of 2:1 under static photolysis.[11] Recently, Jang and coworkers have performed laser flash photolysis experiment and reported that the lifetime of biradical intermediate of **RF** is eight times longer than that of **RH** based on the transient absorption kinetic profiles.[12] They have concluded that the lifetime of the biradical intermediate of *o*-2,2,2-trifluoroethoxybenzophenone (**BRF**) is long enough to achieve conformational equilibrium resulting comparative yield of two diastereomers. Theoretical calculations are useful method to estimating thermodynamic properties of biradical intermediates if direct detection of biradical intermediates is difficult.[13,14] Fang and coworkers have investigated the Norrish type I and II reaction of butyrophenone using complete-active-space self-consistent field (CASSCF) theory and density functional theory (DFT). The authors calculated energies and lifetimes of reaction intermediates including 1,4-biradical intermediate.[13] In this paper, we have performed quantum chemical calculation using density fuctional theory to optimize geometries and energies of the each chemical species involved in the photochemical reaction of *o*-ethoxybenzophenone (**RH**) and *o*-2,2,2-trifluoroethoxybenzophenone (**RF**) using Gaussian 03 package of programs[15] based on the previous reports that B3LYP method has demonstrated efficient reproducibility of the observed structures, barrier heights, and transition energies of biradical intermediates.[16-20] The aim of this study is to understand final branching ratios of the diastereomers shown in Figure 1 in the view of energy aspect. Figure 2 shows optimized geometries for the reactants, biradicals, and final products in the photochemical reactions of **RF** and **RH** at the B3LYP/6-31G+ level. The distances between oxygen in carbonyl group and hydrogen in CH_2 are less than 3.0 Å for the two reactants (**RH**, **RF**) indicating that hydrogen abstraction is feasible with slight bond rotation since hydrogen abstraction does not occur if the distance between the carbonyl oxygen and hydrogen atom is greater than 3.0 Å.[21] The energies of each geometry optimized species relevant to the photochemical processes of two reactants are shown in



RH ($R=CH_3$) **BRH** ($R=CH_3$) **HTS** ($R=CH_3$) **PH** ($R=CH_3$), Z:E=11:1
RF ($R=CF_3$) **BRF** ($R=CF_3$) **FTS** ($R=CF_3$) **PF** ($R=CF_3$), Z:E=2:1

Figure 1. Photocyclization reaction mechanisms of **RF** and **RH**.

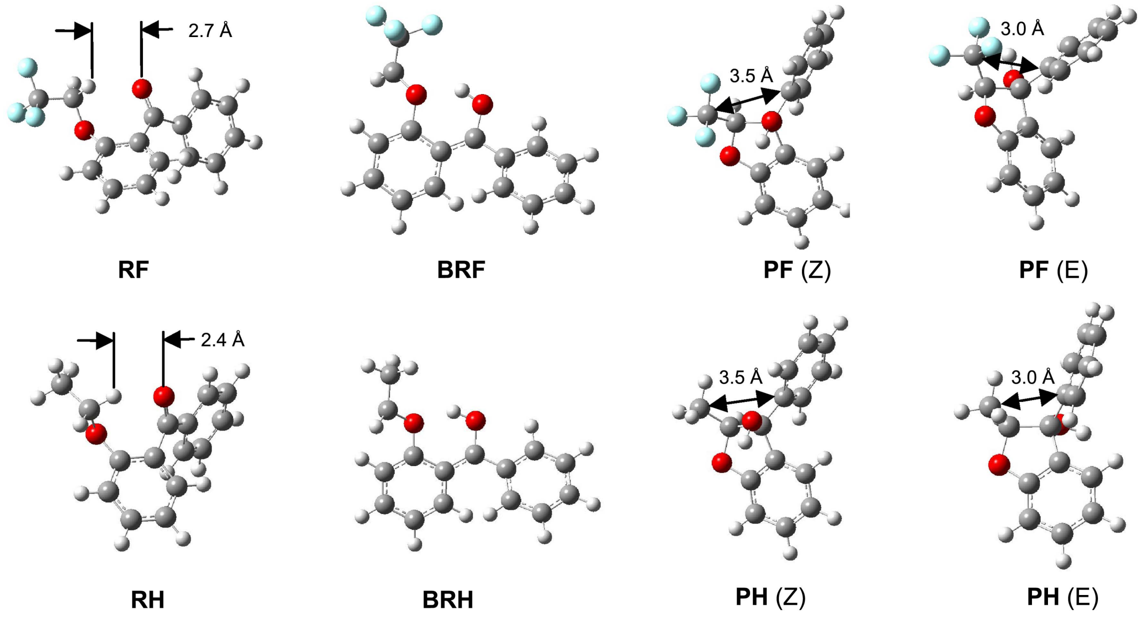


Figure 2. Optimized geometries for the reactants, biradicals, and final products in the photochemical reactions of **RF** and **RH**.

Table 1. Total energies for the species involved in the photochemical reactions of *O*-2,2,2-trifluoroethoxybenzophenone (**RF**) and *O*-ethoxybenzophenone (**RH**). All energies are zero point corrected and given in hatrees

Species	B3LYP/6-31G+	Species	B3LYP/6-31G+
RF	−1027.766475	**RH**	−730.053532
BRF	−1027.663113	**BRH**	−729.795240
FTS-2 (E)	−1027.646938	**HTS-2 (E)**	−729.936037
FTS-2 (Z)	−1027.645231	**HTS-2 (Z)**	−729.944251
PF (E)	−1027.733643	**PH (E)**	−730.052993
PF (Z)	−1027.741508	**PH (Z)**	−730.055503

Table 1. Figure 3 shows relative energetics along with the mechanistic pathways from biradical to final products as shown in Figure 1. It should be noted that 1,5-biradical intermediate also breaks down to enol and ethylene or disproportionates back to reactant species although these reactions were not considered in the present study.[22,23] According to the relative energy differences between reactants and products, both reactions are endothermic while both Z forms are relatively stable as compared to E forms. Relative stability of the cyclized products (**PF**, **PH**) might be understood by the comparison of the distance between methyl group and phenyl group in the cyclized product since repulsive interaction between methyl group and phenyl group is expected to be larger than that between methyl and OH group. As shown in Figure 2, the distances between methyl and phenyl group in the cyclized products are found to be 3.0 Å in Z form and 3.5 Å in E form, respectively, consistent with relative stability of Z form as compared to E form for both cyclized products. The energy difference between Z and E form is larger in **PF** (4.9 kcal/mol) than in **PH** (1.6 kcal/mol) because repulsive interaction between phenyl group and CF_3 in **PF** tends to destabilize E form to a greater extent as compared to CH_3 in **PH**. If final branching

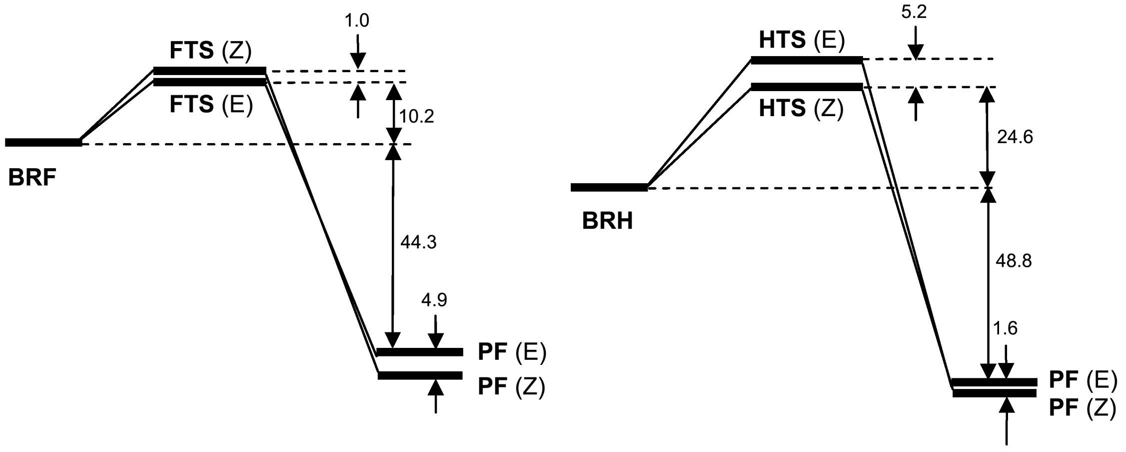


Figure 3. Relative energy diagrams for the photochemical reaction of **RF** and **RH** from biradical to final products. All energies are zero-point corrected and given in kcal/mol.

ratio is solely determined by the relative stability of diastereomers, Z form will be dominant in **PF**, which is in conflict with static photolysis result that Z form was dominant in **PH**. This indicates that the final branching ratios of the cyclized products depend not only on the relative stabilities of the final products but also on the energy barriers leading to the final products. In order to form five-membered ring by cyclization from biradical intermediate, it must overcome large energy barrier resulting from ring strain caused by bulky groups directly attached to radical centers. Based on a comparison between energy barriers leading to the final products as shown in Figure 3, the energy barrier for Z form is slightly higher (1.0 kcal/mol) than E form in **PF**, whereas the energy barrier for Z form is lower (5.2 kcal/mol) than E form in **PH**. Therefore, relatively low energy barrier of Z form in **PH** is responsible for the dominance of Z form in the static photolysis experiment even if relative stability of Z form in **PH** is lower than **PF**. On the basis of previous studies on the cyclization mechanism, a diastereomeric ratio of cyclized products can be determined before or during cyclization by energies associated with transition states and final products. If energy difference between transition states for cyclization is larger than the energy difference between final products, a diastereomeric ratio of the final products is determined before cyclization.[21,24] In this case, diastereomeric ratio will depend on the relative stability of transition states rather than the energy difference between final products. Photochemical pathway of **PH** belongs to this category and results in dominance of Z form. On the other hand, if energy difference between transition states for cyclization is smaller than the energy difference between final products, diastereomeric ratio is determined during cyclization. In this case, diastereomeric ratio will be determined by the combination of energy difference between final products and energy difference between transition states for cyclization. Photochemical pathway of **PF** belongs to this category resulting comparative diastereomeric ratio of cyclized products. We note here that solvent effect was not considered in this study. In the flash photolysis experiments, small amount of pyridine was added to cyclohexane in order to stabilize the biradical intermediates because detecting biradical intermediate is very difficult.[25] Even if static photolysis experiment was performed under different solvent (benzene), these two photolysis experiments were in qualitative agreement suggesting that the relative energy orderings of the species involved in the reactions does not change by solvent effect. An accurate kinetic model along with the energy landscapes calculated in this study including complicated solvent effects can elucidate quantitative results of the previous photolysis experiments and will be a subject of the future publication.[26] In summary, we have calculated energies of the chemical species involved in the photochemical reaction of *o*-ethoxybenzophenone (**RH**) and *o*-2,2,2-trifluoroethoxybenzophenone (**RF**) by carrying out DFT calculations at the B3LYP/6-31G+ level. The energy difference between two diastereomers in **PF** is calculated to be larger than **PH** because E form in **PF** is relatively unstable due to repulsive interaction between CF_3 and phenyl group. On the basis of the energy difference between transition states for cyclization and the energy difference between final products, diastereomeric ratio is determined during cyclization in **PF** and before cyclization in **PH**. Theoretical calculations are in qualitative agreement with previous photolysis experiments.

Computational Details

Optimized geometries and energies of closed- and open-shell species were calculated using restricted and unrestricted Becke's three parameter hybrid method employing LYP correction function (B3LYP) with the 6-31G+ basis set, respectively. Vibrational frequencies were calculated at same level of theory and basis set for all of the stationary points in order to obtain corrections for the zero point energies (ZPEs). Frequency calculations for the transition states in the photochemical process resulted in one imaginary frequency for each species.

References

1. Scaiano, J. C. *Acc. Chem. Res.* **1982**, *15*, 252-258.
2. Ayitou, A. J.-L.; Jesuraj, J. L.; Barooah, N.; Ugrinov, A.; Sivaguru, J. *J. Am. Chem. Soc.* **2009**, *131*, 11314-11315.
3. Angew. *Chem.* **1991**, *30*, 1387.
4. Hu, S.; Neckers, D. C. *J. Org. Chem.* **1997**, *62*, 7827-7831.
5. Singhai, N.; Koner, A. L.; Mai, P.; Venugopaian, P.; Nau, W. M.; Moorthy, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 14375-14382.
6. Katritzky, A. R.; Zerner, M. C.; Karelson, M. M. *J. Am. Chem. Soc.* **1986**, *108*, 7213-7214.
7. Abad, S.; Bosca, F.; Domingo, L. R.; Gil, S.; Pischel, U.; Miranda, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7407-7420.
8. Melikyan, G. G.; Voorhees, E.; Wild, C.; Spencer, R.; Molnar, J. *Tetrahedron Lett.* **2010**, *51*, 2287-2290.
9. Lhiaubet-Vallet, V.; Bosca, F.; Miranda, M. A. *J. Phys. Chem. B* **2007**, *111*, 423-431.
10. Schmidt, B.; Kunz, O.; Biernat, A. *J. Org. Chem.* **2010**, *75*, 2389-2393.
11. Kim, T. Y.; Park, B. S. *Bull. Korean Chem. Soc.* **1997**, *18*, 141-142.
12. Kim, H.; Park, B. S.; Jang, D.-J. *J. Photoch. Photobio. A* **2011**, *218*, 174-177.
13. He, H.-Y.; Fang, W.-H.; Philips, D. L. *J. Phys. Chem. A* **2004**, *108*, 5386-5392.
14. Wood, G. P. F.; Moran, D.; Jacob, R.; Radom, L. *J. Phys. Chem. A* **2005**, *109*, 6318-6325.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 03*, Revision E.01.; Gaussian, Inc.: Pittsburgh, PA, 2003.

16. Kwon, O.; Chung, G. *Bull. Korean Chem. Soc.* **2008**, *29*, 2140-2144.
17. Goddard, J. D.; Chen, X.; Orlova, G. *J. Phys. Chem. A* **1999**, *103*, 4078
18. Goddard, J. D.; Orlova, G. *J. Chem. Phys.* **1999**, *111*, 7705.
19. Beno, B. R.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 4816.
20. Li, Y.; Houk, N. *J. Am. Chem. Soc.* **1993**, *115*, 7478-7485.
21. Wagner, P. J.; Meador, M. A.; Zhou, B.; Par, B.-S. *J. Am. Chem. Soc.* **1991**, *113*, 9630-9639.
22. Turro, N. J. *Modern Molecular Photochemistry*; The Benjamin/Cummings Publishing Company: InC., Menlo Park, California, 1991; p 386.
23. Singhal, N.; Koner, A. L.; Mal, P.; Venugopalan, P.; Nau, W. M.; Moorthy, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 14375-14382.
24. Lewis, F. D.; Hilliard, T. A. *J. Am. Chem. Soc.* **1972**, *94*, 3852-3858.
25. Wagner, P. J.; Kelso, P. A.; Kemppainen, A. E.; McGrath, J. M.; Schott, H. N.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7506-7512.
26. Shen, L.; Fang, W.-H. *J. Org. Chem.* **2011**, *76*, 773-779.