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

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Biradical intermediates, produced via Norrish type II reaction, play an important role in many chemical reactions. 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. It is well-known that substituent groups attached to radical centers greatly influence the branching ratio of the final products. 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. When a biradical intermediate is stereogenic, diastereoselectivity can be created in the course of cyclization by the rotation of a single bond. In the field of organic chemistry, diastereoselective synthesis is important because the reactions of synthetic drugs with biomolecules are often stereoselective. 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. 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. 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. 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. In this paper, we have performed quantum chemical calculation using density functional 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 based on the previous reports that B3LYP method has demonstrated efficient reproducibility of the observed structures, barrier heights, and transition energies of biradical intermediates. 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 CH2 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. The energies of each geometry optimized species relevant to the photochemical processes of two reactants are shown in

Figure 1. Photocyclization reaction mechanisms of RF and RH.
Table 1. 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.\textsuperscript{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\textsubscript{3} in PF tends to destabilize E form to a greater extent as compared to CH\textsubscript{3} in PH. If final branching

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 hartrees

<table>
<thead>
<tr>
<th>Species</th>
<th>B3LYP/6-31G+</th>
<th>Species</th>
<th>B3LYP/6-31G+</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>−1027.766475</td>
<td>RH</td>
<td>−730.053532</td>
</tr>
<tr>
<td>BRF</td>
<td>−1027.663113</td>
<td>BRH</td>
<td>−729.795240</td>
</tr>
<tr>
<td>FTS-2 (E)</td>
<td>−1027.646938</td>
<td>HTS-2 (E)</td>
<td>−729.936037</td>
</tr>
<tr>
<td>FTS-2 (Z)</td>
<td>−1027.645231</td>
<td>HTS-2 (Z)</td>
<td>−729.944251</td>
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<tr>
<td>PF (E)</td>
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<td>PH (E)</td>
<td>−730.052993</td>
</tr>
<tr>
<td>PF (Z)</td>
<td>−1027.741508</td>
<td>PH (Z)</td>
<td>−730.055503</td>
</tr>
</tbody>
</table>

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

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**