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Studies on the *C/O*–regioselectivity in Electrophilic Fluoromethylations of β-Ketoesters based on Thermodynamics by *Ab initio* Calculations

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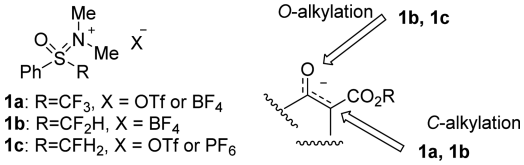
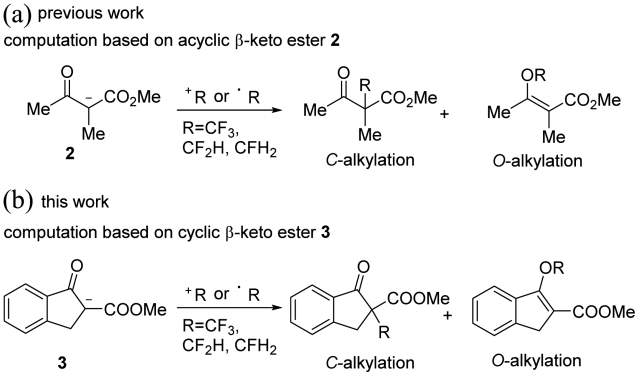
Keto-enol interconversion is one of the most common known tautomerizations in carbonyl compounds, such as β-ketoesters. Due to the simultaneous exisitence of both keto-form and enol-form, carbonyl compounds generally own ambident reactivity on the carbon and oxygen sites. And the control of *C/O*-regioselectivity in the alkylation of enolates hence became a historic research problem in organic chemistry.[1-3] The ratio of regioisomers formed by *C/O*-alkylation is sensitive to the extent of substrate enolization, which is highly dependent on the structure of carbonyl compounds and the reaction conditions, in particular the solvents and bases. For example, for the 1,3-dicarbonyl compounds, nonpolar, aprotic solvents generally favor the enol form due to the intramolecular hydrogen bond formed, while the keto form would be enhanced in polar solvents, especially in protic solvents, since this tautomer is more preferred to be solvated or form intermolecular hydrogen bonds with the solvent molecules. The unequal distribution of the tautomers and negative charge would then affect the formation of *C*-alkylated and *O*-alkylated products. And the nature of the alkylating reagents was also identified to have a significant influence on the *C/O* regioselectivity in resulting products. It has been shown that more *C*-alkylation tends to be observed with softer electrophiles, whereas *O*-alkylation is favoured with harder electrophiles.[4-7] However, the complete control of *C/O* regioselectivity is still a challenge, for example, the regioselective *O*-methylation of β-ketoesters.[8,9] In addition, the introduction of a fluoromethyl group into organic compounds is extraordinarily attractive because it may enhance the lipophilicity and biologically activity of the parent molecules.[10-12] Fluorinated sulfoxinmines and sulfoximinium salts are important structures in the fluoroalkylation of organic compounds.[13,14] During our research with this kind of reagents, we came across unique phenomena for *C/O*-selectivity in the electrophilic fluoromethylation reactions. Namely, the *C/O* regioselectivity on the electrophilic tri-, di- and monofluoromethylation of β-ketoesters with fluorinated methylsulfoxinium salts **1a-c** was highly dependent on the number of fluorine atoms in the fluoromethyl group (Scheme 1). While complete *C*-alkylation was observed in the electrophilic trifluoromethylation using **1a**,[14j] *O*-alkylation predominantly occurred in the electrophilic monofluoromethylation reaction by **1c**.[14f] Besides, a mixture of *C*- and *O*-alkylated products was obtained in the difluoromethylation reaction by **1b**.[15] These selectivities are fundamentally observed independent of the substrates structure, reaction conditions including bases, solvents, and reaction temperature. Since the structure of the fluoromethylating reagents, including their counter anions, is also not a critical factor for *C/O*-regioselectivity, the number of fluorine atoms in the fluoromethyl group, CF_xH_{3-x}, seems to be the origin of *C/O*-regioselectivity.

We explained these unique phenomena with the help of *ab initio* calculations based on the simple model of acyclic β-ketoester anion **2**, and we concluded that the trifluoromethylation involves the formation of $^{+}CF_3$ under this reaction condition to provide complete *C*-alkylated products, while monofluoromethylation proceeds involving a radical-like species such as $^{\bullet}CFH_2$ to furnish complete *O*-alkylated pro-



Scheme 1. *C/O*-selectivity of fluoromethylations of β-ketoesters with fluorinated methylsulfoxinium salts **1a-c**.



Scheme 2. Model for computations.

ducts. On the other hand, difluoromethylation could involve both cationic and radical species to afford a mixture of *C*- and *O*-isomers (Scheme 2(a)). In order to further elaborate the *C*/*O* preference in fluoromethylation reactions, we now re-investigate using a cyclic substrate, methyl 1-indanone-2-carboxylate anion **3** based on the thermodynamics by MP2/6-311G** level *ab initio* calculations (Scheme 2(b)). And similar results were obtained which support our proposed mechanism.

Results and Discussion

Ab initio calculations were carried out for studying the reaction of the naked anion of methyl 1-indanone carboxylate **3** with cation or radical species of CF_3, CF_2H, or CFH_2 providing *C*-alkylated or *O*-alkylated products.

First, the most stable rotamer of anion **3** was obtained at the MP2/6-311G** level (Figure 1). The interactions of **3** with $^+CF_3$, $^+CF_2H$ and $^+CFH_2$ cations were next studied by *ab initio* molecular orbital calculations. The geometries of the complexes of **3** with the three cations were optimized. The *C*- or *O*-alkylated products **4-6** were spontaneously generated by the geometry optimizations, which indicates that there exists no potential energy barrier for the formation of the C–C and C–O bonds (Figure 2). The C–C bond was formed with the carbon atom between two carbonyl groups of **3**. The C–O bond was formed with an oxygen atom of the carbonyl group. The optimized geometries and relative energies of the products are shown in Figure 2. The calculations show that the *C*-alkylated products are significantly more stable than the *O*-alkylated products. The *O*-alkylated products with the $^+CF_3$ cation (**4b** and **4c**) are 14.01 and 30.54 kcal/mol less stable than the *C*-alkylated product (**4a**), respectively. The *O*-alkylated products with the $^+CF_2H$ (**5b** and **5c**) are 15.64 and 29.73 kcal/mol less stable than the *C*-alkylated products (**5a**), respectively. The *O*-alkylated products with the $^+CFH_2$ (**6b** and **6c**) are 18.19 and 31.42 kcal/mol less stable than the *C*-alkylated products (**6a**), respectively. The larger stability of the *C*-alkylated **4a**, **5a** and **6a** suggests that the reactions of **3** with the cations, $^+CF_3$, $^+CF_2H$, and $^+CFH_2$, prefer to produce *C*-alkylated products independent of the number of fluorine molecules. The complete *C*-regioselectivity for the trifluoromethylation can be explained by the cationic process. This result is similar to the case of the products obtained from the calculations based on an acyclic β-ketoester anion (Scheme 2(a)).[15] This result indicates the electronic character of trifluoromethyl sulfoxinium salt **1a** is different from the dibenzothiophenium salts which were developed by Umemoto. Magnier and coworkers identified a radical pathway should be responsible for the trifluoromethylation of silyl-enol ethers with Umemoto's reagent and they were also confident that this route is involved in the reaction with other soft nucleophiles, such as β-ketoesters.[16]

The geometries of anion **3** complexed with fluoromethyl radicals $^{\bullet}CF_3$, $^{\bullet}CF_2H$, $^{\bullet}CFH_2$ were next investigated (Figure 3). The optimized geometries of complexes **7-9** and the stabilization energies (E_{form}) are shown in Figure 3.[17] The carbon atom of the $^{\bullet}CF_3$ radical that entered into contact with the oxygen atoms of two carbonyl groups was found to be the most stable geometry **7c**. Meanwhile, optimized geometries **8a** and **9a**, in which the hydrogen atoms of $^{\bullet}CF_2H$ or $^{\bullet}CFH_2$ radicals were in contact with the oxygen atoms of the two carbonyl groups, were found to be the most stable. The E_{form} for **8a** and **9a** (–10.52 and –7.69 kcal/mol, respectively) are substantially larger (more negative) than that for **7c** (–4.48 kcal/mol), which shows that the attractive interactions of **3** with $^{\bullet}CF_2H$ and $^{\bullet}CFH_2$ radicals are stronger than that

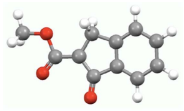


Figure 1. The most stable rotamer of anion **3** at the MP2/6-311G** level.

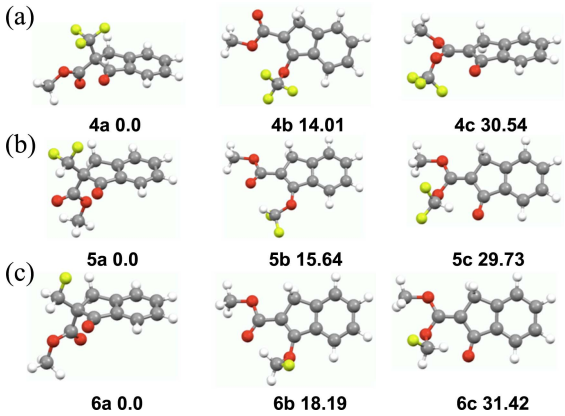


Figure 2. (a) The optimized geometries and relative energies of C–CF_3 product **4a**, and O–CF_3 products **4b** and **4c** at the MP2/6-311G** level. Energy in kcal/mol. (b) The optimized geometries and relative energies of C–CF_2H product **5a**, and O–CF_2H products **5b** and **5c**. (c) The optimized geometries and relative energies of C–CFH_2 product **6a**, and O–CFH_2 products **6b** and **6c**.

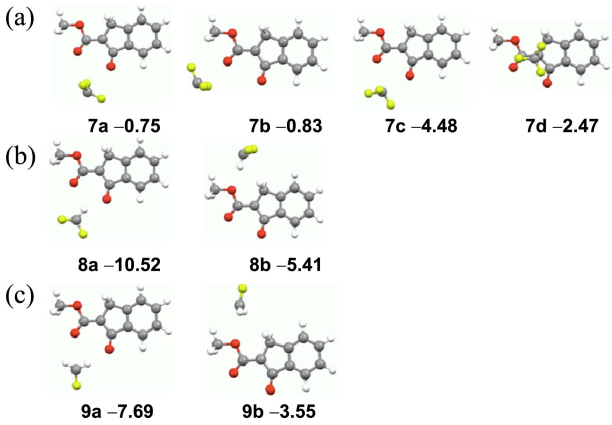


Figure 3. (a) Four optimized geometries of **3** with $^{\bullet}CF_3$ and their stabilization energies at the MP2/6-311G** level. Energy in kcal/mol. (b) Two optimized geometries of **3** with $^{\bullet}CF_2H$ and their stabilization energies. (c) Two optimized geometries of **3** with $^{\bullet}CFH_2$ and their stabilization energies.

with the $^{\bullet}CF_3$ radical. Despite the initial geometries before calculations where the $^{\bullet}CF_2H$ and $^{\bullet}CFH_2$ radicals are located several positions around **3**, the geometries converged to **8a** and **9a** after the optimizations in most cases. The local minimum structures in which the $^{\bullet}CF_2H$ and $^{\bullet}CFH_2$ radicals were in contact with the carbon atom between the two carbonyl groups of **3** were not obtained by the geometry optimizations. These results show that $^{\bullet}CF_2H$ and $^{\bullet}CFH_2$ radicals prefer to locate close to the oxygen atoms of the two carbonyl groups of **3**, producing *O*-alkylated products. The complete *O*-regioselectivity found in the monofluoromethylation can be explained by the radical-like mechanism involving the SET process although the free radical monofluoromethylation is rare.[18] In addition, more recently, Hu *et al.* disclosed that a $^{\bullet}CFH_2$ species was involved in the monofluoromethyltion of *O*-, *S*-, *N*- and *P*- nucleophiles with a monofluorinated sulfoximine, $PhSO(NTs)CH_2F$.[14a] This report would also somewhat support our results. For the difluoromethylation of **3** with **1b**, both cationic and radical processes are suggested based on the above calculations (Figures 2(b) and 3(b)). They are consistent with the computational results based on the acyclic β-ketoester and the experimental results for difluoromethylation of **3** in which a mixture of *O*- and *C*-alkylated products was obtained.[15]

Finally, we attempted the calculations of the methyl 1-indanone-2-carboxylate radical with fluoromethyl radicals $^{\bullet}CF_3$, $^{\bullet}CF_2H$, $^{\bullet}CFH_2$. However, the initial combination of the carboxylate radical and fluoromethyl radicals spontaneously converted into a combination of the anion **3** and fluoromethyl cations, $^{+}CF_3$, $^{+}CF_2H$ and $^{+}CFH_2$ which gave the same results for the calculations of **3** and radicals as mentioned in the first investigation.

Based on the computations, plausible schematic reaction mechanisms for trifluoromethylation and monofluoromethylation are shown in Figure 4. Similar to the mechanism shown in our previous paper,[15] $^{+}CF_3$, would be generated directly from the reagent **1a** with the reaction of **3** *via* SN2-like pathway (Figure 4(a)) providing *C*-alkylated product with dimethylamino phenyl sulfinamide. On the other hand, monofluoromethylation would proceed *via* an attack of the enolate oxygen to the sulfur center of **1b** to afford a sulfurane-type intermediate **TS-I**,[8,9] which collapses into $[CFH_2]^{\bullet}$ and $[PhS(O)NMe_2]^{\bullet+}$ with the regeneration of **3**. The **3** attacks $[CFH_2]^{\bullet}$ to provide *O*-alkylated product *via* **TS-III** (Figure 4(b)).

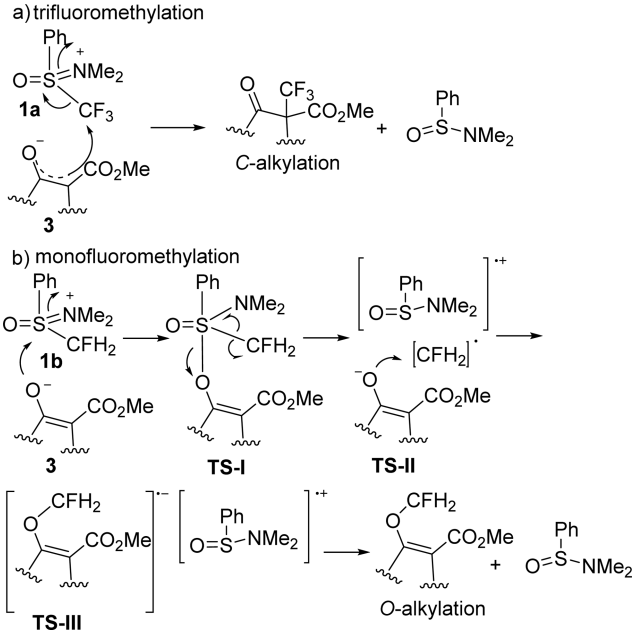


Figure 4. Plausible schematic reaction mechanisms, (a) trifluoromethylation and (b) monofluoromethylation.

Conclusion

In conclusion, the *C/O* regioselectivity in fluoromethylations of β-ketoesters with fluorinated methylsulfoxinium salts **1a-c** was re-investigated based on the thermodynamics by MP2/6-311G** level *ab initio* calculations of the interactions of a cyclic β-ketoester anion **3** with fluoromethyl cations or radicals. The computational results are in accordance with previous results based on an acyclic β-ketoester. This result supports our proposed mechanism and viewpoints regarding the electrophilic fluoromethylation of β-ketoesters. That is, a $^{+}CF_3$ cation is formed and is responsible for the complete *C*-alkylated products in trifluoromethylation, while a more radical-like species such as $^{\bullet}CFH_2$ is possibly generated to furnish *O*-alkylated species in monofluoromethylation. For difluoromethylation, a weaving cationic and radical species participates to afford a mixture of *C*- and *O*-isomers. In the case of difluoromethylation, a difluorocarbene mechanism is also should be concerned, however, Prakash et.al. denied it and suggested electrophilic type reaction.[14g] Although our conclusion is just one of the hypotheses based on the calculations of the thermodynamics, it might be helpful to further the discussion of the reaction mechanism not only about trifluoromethylation but also about *C/O*-regioselectivity in the conventional alkylation of enolates. Further investigation is now on going based on the calculations of transition states.

Experimental

Computational Methods. The Gaussian 03 program[17] was used for the *ab initio* molecular orbital calculations. Electron correlation was accounted for by the second-order Møller-Plesset perturbation (MP2) method.[19,20] The 6-311G** basis set was used for the calculations. The stabilization energy by the formation of a complex from isolated species (E_{form}) was calculated as the sum of the interaction energy (E_{int}) and the deformation energy (E_{def}). E_{def} is the sum of the increase of the energies of monomers by the deformation associated with the formation of the complex. E_{int} was calculated by the supermolecule method. The basis set superposition error (BSSE)[21] was corrected for the interaction energy calculations using the counterpoise method.[22] The geometries of the complexes were optimized from 22 initial geometries. The atomic charges were obtained by electrostatic

potential fitting using the Merz-Singh-Kollman scheme[23,24] from the MP2/6-311G** level wave functions of the isolated molecules.

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