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Complete Reversal in Regioselectivity in the Baeyer−Villiger Reaction of an α-CF_3-Ketone and Theoretical Rationale for Axial Orientation of Sterically Demanding CF_3 Group at the Transition State

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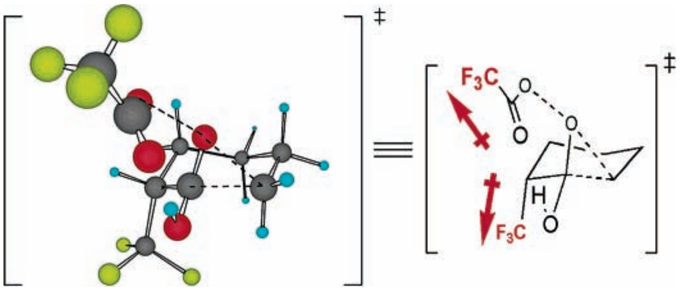
ABSTRACT

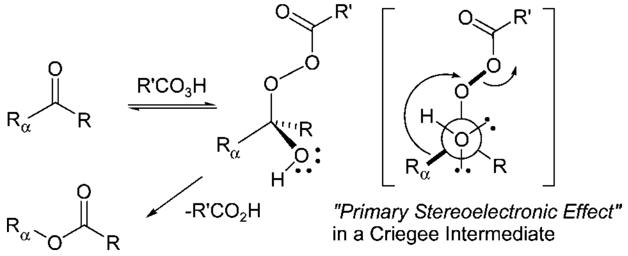


The regioselectivity of the Baeyer−Villiger reaction of α-CF_3-ketone is completely reversed from that in α-F_{eq}-ketone. Theoretical study rationalized that the reaction proceeds with the sterically demanding CF_3 group in an axial orientation by strong dipole interaction. The guiding principle that strong dipole interaction can overcome steric repulsion as a determining factor not only in regio- but also in stereocontrol is proposed.

The Baeyer−Villiger (B−V) reaction[1] has been widely employed in organic synthesis.[2] A two-step mechanism has been well accepted: (1) carbonyl addition of a peroxy acid to form a peroxy acid/carbonyl adduct, the Criegee intermediate[3] and then (2) skeletal rearrangement of the Criegee intermediate. Many kinetic studies have shown that the rearrangement of the Criegee intermediate is a concerted process that is rate determining (Scheme 1).[4]

The stereoelectronic requirement for correct antiperiplanar alignment of the migrating substituent and the O−O bond of the leaving peroxyacid (e.g., R′COO$^-$) has been well accepted and referred to as the primary stereoelectronic effect (parentheses in Scheme 1):[5] the migration of carbon **a** located in the correct antiperiplanar alignment by (i) a conformational

Scheme 1. Baeyer−Villiger Reaction



"Primary Stereoelectronic Effect"
in a Criegee Intermediate

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[1] Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625−3633.

[2] Reviews: (a) Krow, G. R. *Org. React.* **1993**, *43*, 251−798. (b) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, *737*, 7−750. (c) Krow. G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 671.

[3] Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127−135.

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factor[6] or (ii) a stereoelectronic factor by the dipole interaction of α-F$_{eq}$ and the leaving peroxy acid[7] (Figure 1).

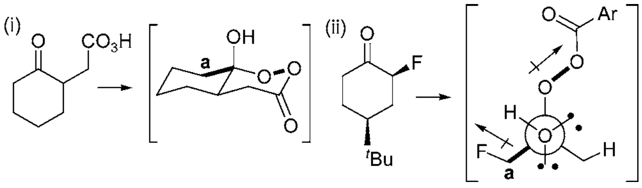
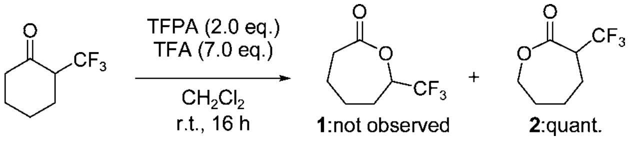


Figure 1. Primary stereoelectronic effect in the Criegee intermediate of (i) Chandrasekhar's and (ii) Crudden's model.

On the basis of the result of Crudden's α-F$_{eq}$-ketone, one might predict that α-CF$_3$-ketones should provide a similar trend for migration of the CF$_3$-bearing carbon because of the equatorial orientation of the sterically demanding CF$_3$ group.[8]

Significantly, however, the B−V reaction of α-CF$_3$-ketone showed the opposite regioselectivity to that of α-F$_{eq}$-ketone. The B−V reaction of α-CF$_3$-cyclohexanone was examined using trifluoroperacetic acid (TFPA) as an oxidant. When α-CF$_3$-cyclohexanone was treated with TFPA and trifluoroacetic acid (TFA) in CH$_2$Cl$_2$, migration was observed only at the carbon without the CF$_3$ group to afford the product quantitatively (Scheme 2).[9,10]

Scheme 2. B−V Reaction of α-CF$_3$-Cyclohexanone



The regioselectivity was further examined with acidic or basic additives employing *m*CPBA as an oxidant,[11] because *m*CPBA alone gives only a trace amount of the product (8% after 3 days, Table 1, entry 1).[12] Indeed, the same regioselectivity was obtained with significant acceleration by the use of Sc(OTf)$_3$ (entry 4) or TfOH (entry 6), in particular.[13]

Therefore, we theoretically examined the rearrangement step to illustrate the origin of the regioselectivity of the B−V reaction of an α-CF$_3$-cyclohexanone.[14] The B−V reaction of α-CF$_3$-cyclohexanone by TFPA was examined at the MP2/6-31G**//HF/6-31G* level.[15−17] As shown in Figure 2, there were a total of eight possible conformations in the chemical model of the rearrangement step with respect to the orientation (axial or equatorial) of the oxidant and CF$_3$ group and the regioselectivity of the migrating carbon (path ***a*** or ***b***) (Figure 2). The relative energies are shown in Table 2, and

Table 1. Effect of Various Additives in B−V Reaction of α-CF$_3$-Cyclohexanone

entry	additive [equiv]	time	**1** [% yield][a]	**2** [% yield][a]
1		3 days		8
2	NaHCO$_3$ [2.0]	10 days		15
3	Yb(OTf)$_3$ [1.2]	3 days		10
4	Sc(OTf)$_3$ [1.2]	5 h		91
5	TFA [1.0]	2 days		11
6	TfOH [1.0]	1 h		91

[a] Determined by ^{19}F NMR using BTF as an internal standard.

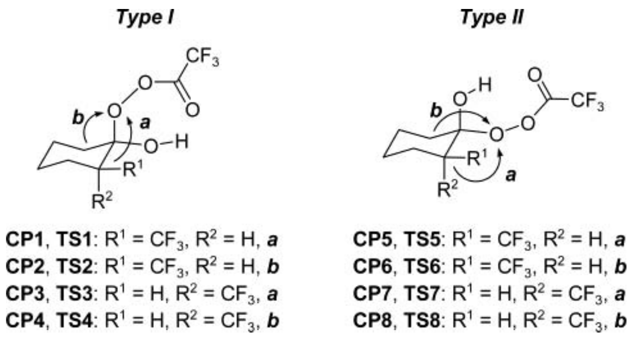


Figure 2. Two types of the reaction model.

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(4) (a) Hawthorne, M. F.; Emmons, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 6398−6404. (b) Palmer, B. W.; Fry, A. *J. Am. Chem. Soc.* **1970**, *92*, 2580−2581. (c) Mitsuhashi, T.; Miyadera, H.; Simamura, O. *J. Chem. Soc., Chem. Commun.* **1970**, 1301−1302. (d) Winnik, M. A.; Stoute, V. *Can. J. Chem.* **1973**, *51*, 2788−2793. (e) Winnik, M. A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* **1974**, *96*, 1977−1979.

(5) Correct antiperiplanar alignment of the lone electron pair of the hemiacetal oxygen and the migrating substituentes is also proposed for the migration step. (a) Noyori, R.; Sato, T.; Kobayashi, H. *Tetrahedron Lett.* **1980**, *21*, 2569−2572. (b) Noyori, R.; Kobayashi, H.; Sato, T. *Tetrahedron Lett.* **1980**, *21*, 2573−2576.

(6) Chandrasekhar, S.; Roy, C. D. *Tetrahedron Lett.* **1987**, *28*, 6371−6372.

(7) Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2852−2855

(8) A-value: i-Pr $\approx$ 2.15, CF$_3$ = 2.4−2.5, t-Bu > 4 (kcal/mol). Jensen, F. R.; Bushweller, C. H. *Adv. Alicycl. Chem.* **1971**, *3*, 139−195.

(9) Typical experimental procedure using TFPA. To TFPA (0.2 mmol, 0.6 mL, prepared from trifluoroacetic anhydride and 60% aqueous H$_2$O$_2$) was added dichloromethane (0.4 mL) at room temperature. Then, 2-trifluoromethyl-cyclohexanone (16.6 mg, 0.1 mmol) was added to the mixture at this temperature. After the mixture was stirred for 16 h at this temperature, BTF (10 μL, 0.082 mmol) was added. Spectral analysis by ^{19}F NMR of the reaction mixture showed quantitative yield of 2-trifluoromethyl-6-hexanolide. The product could be isolated by silica gel column chromatography (CH$_2$Cl$_2$) in 89% yield.

(10) In the case of α-CF$_3$-cyclopentanone, the reactivity was lower (78% yield; reaction time was 66 h) but with the same regioselectivity as α-CF$_3$-cyclohexanone. In the case of 7-trifluoromethyl-6-undecanone (a cyclic substrate), the reactivity was significantly lowered (8% yield; 4.2 equiv of TFPA was used, and the reaction time was 5 days), as usually observed in B−V reaction of acyclic ketone, but with the same selectivity as α-CF$_3$-cyclohexanone.

(11) Typical experimental procedure using *m*CPBA. To a solution of *m*CPBA (80% purity) (43.1 mg, 0.2 mmol) and TfOH (8.8 μL, 0.1 mmol) in dichloromethane was added 2-trifluoromethyl cyclohexanone (16.6 mg, 0.1 mmol) at room temperature under an argon atmosphere. After the mixture was stirred for 1 h at this temperature, BTF (10 μL, 0.082 mmol) was added. Spectral analysis by ^{19}F NMR of the reaction mixture showed 91% yield of 2-trifluoromethyl-6-hexanolide.

(12) Various oxidants (TBHP, aqueous H$_2$O$_2$, *m*CPBA, H$_3$PO$_5$) were examined, but only *m*CPBA (8% yield) and H$_3$PO$_5$ (quantitative yield) gave the product.

(13) Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, 462−464.

Table 2. Relative Energies of **CP**s and **TS**s (kcal/mol)

Type I	E_{rel} [kcal/mol]		E_{rel} [kcal/mol]
CP1	0	**TS1**	24.8
CP2	3.4	**TS2**	26.2
CP3	1.3	**TS3**	28.3
CP4	1.4	**TS4**	23.7
Type II	E_{rel} [kcal/mol]		E_{rel} [kcal/mol]
CP5	0.6	**TS5**	26.9
CP6	4.4	**TS6**	26.3
CP7	2.7	**TS7**	26.8
CP8	1.2	**TS8**	24.7

the energy profiles of Type I are shown in Figure 3. The most stable Criegee intermediate was **CP1** (CF_3 = eq, oxidant = ax; path ***a***), which causes the migration of the carbon-bearing CF_3 group as expected on the basis of the α-F_{eq}-ketone. In sharp contrast, the most stable transition state was **TS4** with a sterically demanding CF_3 group in axial orientation (oxidant = ax; path ***b***) in agreement with the experimental result.[18]

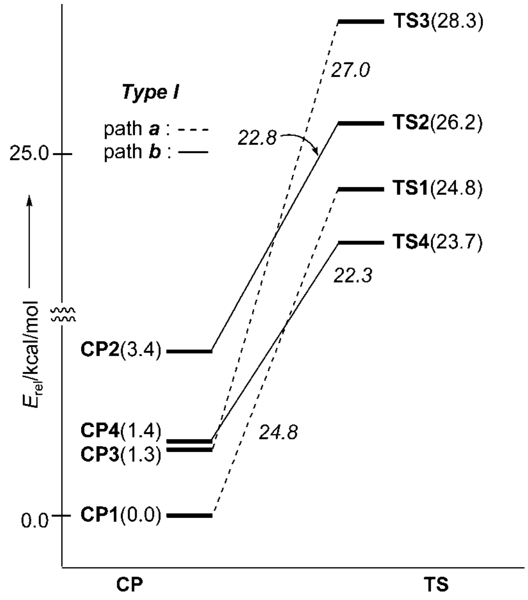

Figure 3. Energy profiles of the B−V reaction at the rearrangement step at the MP2/6-31G**//HF6-31G* level (Type I). The numbers in parentheses are relative energy levels. The activation energies are in italics.

Among the Criegee intermediates, **CP1** has the lowest energy and **CP2** has the highest one. As shown in Figure 4, two CF_3 groups were located at a nearly 180° angle to stabilize **CP1** by dipole interaction in contrast to the nearly 0° angle in **CP2**. In addition, the hydrogen bonding between hemiacetal hydrogen and fluorine exists only in **CP1** but not in other **CP**s.[19] Energy profiles of Type I series (Figure 3) could be sharply classified in path ***a*** (dotted line) and path ***b*** (solid line) in terms of the activation energy. The activation energy of path ***a*** is higher than that of path ***b*** because of the

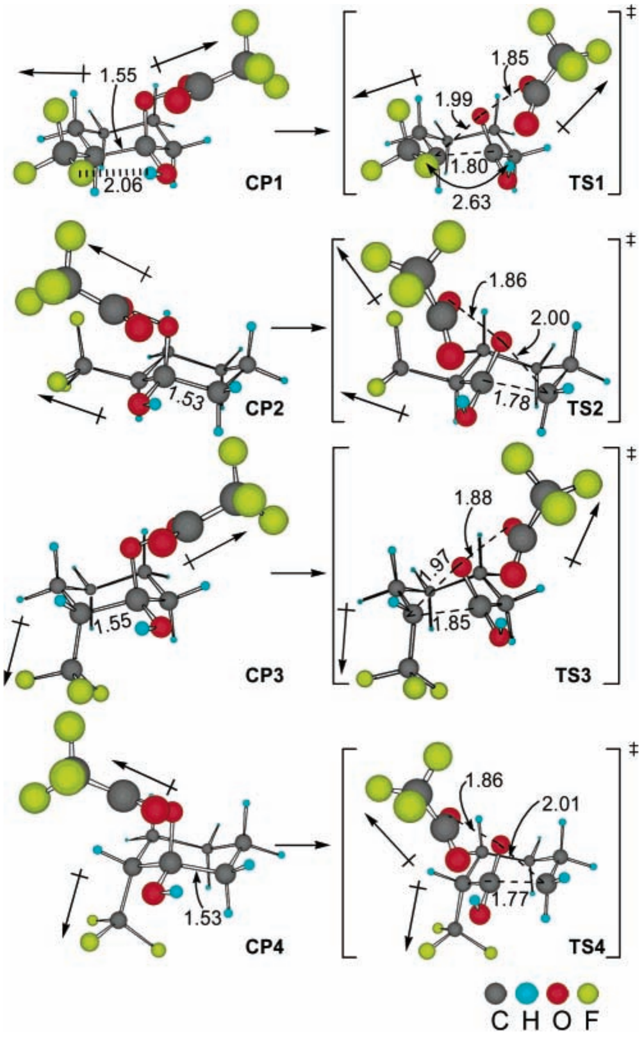

Figure 4. Three-dimensional structure of **CP1**, **TS1**, **CP4**, and **TS4**. The numbers are the distances in Å.

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(14) There are some theoretical studies of the B−V reaction: (a) Stoute, V. A.; Winnik, M. A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1974**, *96*, 6388−6393. (b) Hannachi, H.; Anoune, N.; Arnaud, C.; Lantéri, P.; Longeray, R.; Chermett, H. *J. Mol. Struct.* **1998**, *434*, 183−191. (c) Cádenas, R.; Reyes, L.; Lagúnez-Otero, J.; Cetina, R. *J. Mol. Struct.* **2000**, *497*, 211−225. (d) Cárdenas, R.; Cetina, R.; Lagúnez-Otero, J.; Reyes, L. *J. Phys. Chem.* **1997**, *101*, 192−200. (e) Okuno, Y. *Chem. Eur. J.* **1997**, *3*, 212−218. (f) Eklund, P. R.; Brinck, T. *J. Org. Chem.* **2001**, *66*, 1193−1199.

(15) All calculations were performed using the Gaussian 98 program package (Gaussian, Inc.: Pittsburgh, PA, 1998).

(16) Reference 14e was referred to in determining the calculation level. In reference 14e, the difference between HF/3-21G and MP2/6-31G* was examined in the case of the B−V reaction of formaldehyde by performic acid as the model study. The result of the structural difference was only 3%. Therefore, MP2/6-31G**//HF/6-31G* (higher level than HF/3-21G) was employed in this study.

(17) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986; see also references therein.

(18) Attempt to lock the orientation of the CF_3 group by introducing bulky ^{t}Bu at the 4-position of the cyclohexanone ring failed because of the rapid epimerization of the CF_3 group.

(19) Length of H−F (2.06 Å) in **CP1** is shorter than the sum of H and F van der Waals radii (2.60 Å).

lower nucleophilicity of the carbon adjacent to the CF_3 group by the strong electron-withdrawing nature of the CF_3 group. Curtin−Hammet kinetics[20] should operate in the B−V reaction of the α-CF_3-ketone, and hence the reaction should occur via **TS4**. It is noted that the most stable **TS4** has the axial orientation of the sterically demanding CF_3 group, which is usually located in the equatorial orientation due to the 1,3-diaxial repulsion (Figure 4). The energy level of **TS2** with the CF_3 group in equatorial orientation is higher than that of **TS4**. This indicates that the strong dipole interaction between two CF_3 groups is more effective than the steric repulsion.

In summary, we have illustrated experimentally and theoretically that the B−V reaction of an α-CF_3-ketonic substrate proceeded with regioselectivity opposite to that of α-F_{eq}-ketone. In addition, at the transition state, the sterically demanding CF_3 group is oriented in the axial position due to the strong dipole/dipole interaction of the two CF_3 groups.[21] Thus, we might propose the guiding principle that the dipole interaction can overcome the steric repulsion in the transition state for regio- or stereoselective reaction.

Acknowledgment. Generous allotment of computational time from the Institute for Molecular Science, Okazaki, Japan, is greatly acknowledged.

Supporting Information Available: NMR spectral data of the B−V product, a detalied experimental procedure, and Cartesian coordinates of the calculation model. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111−128. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 648 and references therein.

[21] Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, in press.