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Theoretical Study of the Nucleophilic 5-*Endo-Trigonal* Cyclization of 1,1-Difluoro-1-alkenes

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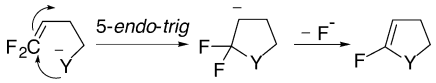
The nucleophilic 5-*endo-trigonal* cyclization of 1,1-difluoro-1-alkenes has been studied at the B3LYP/6-31+G(d) level in an Onsager continuum model for DMF. The reaction takes an addition−elimination path. Both the transition-state structures and the IRC analyses suggest the delocalization of the negative charge to highly electronegative two fluorine atoms during the addition reaction is the origin of the high reactivity of 1,1-difluoro-1-alkenes. Judging from the activation energies, both dichloro and dibromo counterparts are much less reactive for 5-*endo-trigonal* cyclization. In these substrates, the cyclization reaction is promoted by chlorine or bromine atom with their good leaving-group ability, and the addition of oxyanion to the π-bond occurs along with the simultaneous elimination of halogen atom. The study on the cyclizations of β-monofluoro-*o*-hydroxystyrenes and β-bromo-β-fluoro counterparts shows that one fluorine atom is not enough to delocalize the negative charge in the addition step.

Introduction

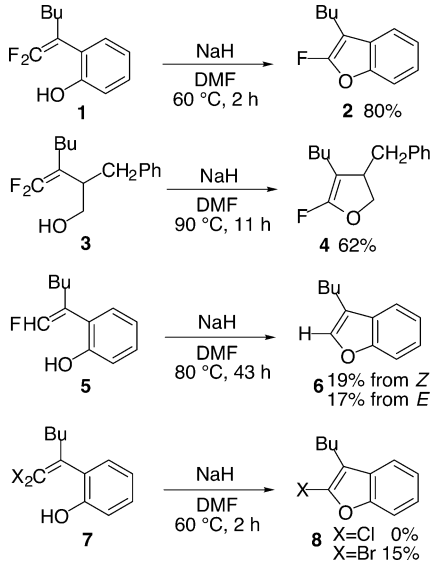
The 5-*endo-trigonal* cyclization is considered to be a disfavored process for the construction of five-membered-rings because of severe distortions in the reaction geometry (Baldwin's rule).[1] Although efficient radical-initiated cyclizations have been devised for the construction of heterocyclic compounds,[2] the corresponding nucleophilic cyclizations are still rarely observed.[3] Taking advantage of the unusual reactivity of 1,1-difluoro-1-alkenes and the leaving-group ability of the fluoride ion, nucleophilic 5-*endo-trigonal* cyclizations were recently realized by Ichikawa and co-workers (Schemes 1 and 2).[4,5] When hydroxystyrene **1** was treated with sodium hydride in dimethylformamide (DMF), the 5-*endo-trigonal* cyclization occurred leading to 2-fluorobenzo[*b*]furan **2** in 80% yield. The cyclization of homoallyl alcohols **3** also afforded

SCHEME 1



Scheme 1

SCHEME 2



5-fluoro-2,3-dihydrofurans **4** in good yields. On the other hand, the corresponding monofluoro compounds **5** gave low yields of the cyclization product **6** after prolonged reaction time. These results revealed that two vinylic fluorine atoms are essential to activate the alkene sufficiently for the nucleophilic 5-*endo-trigonal* cyclization. Both dichloro- and dibromo-*o*-hydroxystyrenes **7a** and **7b** gave poor results even though chloride and

(1) (a) Baldwin, J. E. J. Chem. Soc., *Chem. Commun*. **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun*. **1976**, 736.

(2) (a) Parson, A. F. *C. R. Acad. Sci*. **2001**, *4*, 931 and references therein. (b) Bommezijn, S.; Martin, C. G.; Kennedy, A. R.; Lizos, D.; Murphy, J. A. *Org. Lett*. **2001**, *3*, 3405. (c) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695.

(3) (a) Beak, P.; Wilson, K. D. *J. Org. Chem*. **1986**, *51*, 4627. (b) Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc*. **1988**, *110*, 1617. (c) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem*. **1987**, *52*, 2523. (d) Gao, J.; Rusling, J. F. *J. Org. Chem*. **1998**, *63*, 218. (e) Caldwell, J. J.; Craig, D.; East, S. P. *Synlett* **2001**, 1602. (f) Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem*. **2000**, 903. (g) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett*. **1985**, *26*, 4455. (h) Grigg, R.; Kemp, J.; Malone, J. F.; Rajviroongit, S.; Tangthongkum, A. *Tetrahedron* **1988**, *44*, 5361.

(4) (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun*. **1997**, 1537. (b) Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun*. **2000**, 1887. (c) Ichikawa, J.; Wada, Y.; Sakoda, K. *Chem. Lett*. **2002**, 282. (d) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917.

(5) Et_2NSF_3-catalyzed cyclization of 1,1-difluoroallylic alcohol and its ab initio study was reported: Yamazaki, T.; Hiraoka, S.; Sakamoto, J.; Kitazume, T. *J. Phys. Chem. A* **1999**, *103*, 6820.

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bromide ions are better leaving groups compared to fluoride ion.

To better understand these 5-*endo*-*trigonal* cyclizations and the origin of the high reactivity of 1,1-difluoro-1-alkenes, we decided to study the reaction mechanism computationally. Recently, we reported a theoretical study on the intramolecular amination of chiral bromoallenes on treatment with sodium hydride in DMF and showed that the experimental results have been well rationalized by DFT calculations [B3LYP/6-31+G(d)] and the Onsager solvation model.[6] Furthermore, as our calculations predicted, the improvement of *cis*-selectivities up to 99:1 has been realized by changing the solvent from DMF to THF. Since the method [B3LYP/6-31+G(d),SCRF(Dipole,solvent = DMF)] can explain the nucleophilic reaction on treatment with sodium hydride in DMF well, we applied this method to the above 5-*endo*-*trigonal* cyclizations. Here, we report the results of density functional study using the Onsager solvation model.

Calculation Methods

All calculations were performed using the Gaussian 98 program.[7] Gibbs free energies are the values at 298.15 K and 1.00 atm obtained from the frequency calculations. The thermal energy corrections are not scaled.[8] Vibrational frequency calculations gave only one imaginary frequency[9] for all transition structures and confirmed that those structures are authentic transition structures. The transition state structures were located by the B3LYP hybrid functional[10] together with the 6-31+G(d) basis and the Onsager continuum model[11] for DMF (ϵ = 37.06). After rough potential energy surfaces were drawn by using opt = addredun keyword, the transition structures were obtained starting from the structures near the saddle points by using opt = ts keyword. Starting from the transition-state structures, the reaction paths were followed by an intrinsic reaction coordinate (IRC) analysis.[12] The structures of the reactants, products, and intermediates were obtained by the optimization of the last structures on both sides of the IRC calculations. The frequency jobs on their structures gave only harmonic frequencies and confirmed that they are minima.

Results and Discussion

5-*Endo-Trigonal* Cyclization of β,β-Difluoro-α-methyl-*o*-hydroxystyrene. Since DMF is a polar aprotic solvent, it is able to dissolve many salts and tends to surround metal cations rather than nucleophilic anions. Therefore, the cyclization reaction of the anion **9** derived from β,β-difluoro-α-methyl-*o*-hydroxystyrene was chosen as a model system for the reaction of **1** on treatment with sodium hydride in DMF. The transition state structure **9-ts1** for the nucleophilic 5-*endo*-*trigonal* cyclization of **9** was located in the gas phase (Figure 1). The distance of the forming O−C bond is 1.94 Å, while the distance of the C1−C2 bond increases by 0.05 Å. The activation energy is 19.9 kcal/mol, and the resulting adduct anion **9-int** has a completely flat ring structure. The distances of C−F and C1−C2 bonds are 1.44 and 1.45 Å, respectively, which suggest the delocalization of the negative charge of a carbanion to highly electronegative fluorine atoms. From **9-int**, a cleavage of the C−F bond occurs and a loose complex **9-pr** (2-furobenzo[*b*]furan and F^-) forms. The transition structures for the cyclization of **9** were also located in a self-consistent reaction field (SCRF) for DMF (see italic numbers in Figure 1). The activation energy is 21.3 kcal/mol, and the distance of the forming C−O bond is 1.93 Å. Both the energies and the structures of **9**, **9-ts1**, and **9-int** are almost the same as those in the gas phase. The largest changes are found in **9-ts2**, where the distance of the breaking C−F bond is 1.97 Å (shorter than that in the gas phase by 0.57 Å) and the activation energy is 7 kcal/mol less than that in the gas phase. These values show the cleavage of the C−F bond is a much easier process in a polar solvent. Since two separate species, 2-furobenzo[*b*]furan and F^-, form in SCRF, the energy of **9-pr** was calculated by combining the energies of 2-furobenzo[*b*]furan and F^-. For comparison, the gas-phase transition structure for the reaction of **9** was located by RHF/6-31+G(d) (Figure 2).

To see the effect of two fluorine atoms on the reactivity in the 5-*endo*-*trigonal* cyclization, the reactions of the anions **10a,b** derived from the dichloro and dibromo counterparts were studied computationally (Figure 1). The activation energies for the cyclization of the dichloro and dibromo anions **10a** and **10b** are 27.0 and 26.7 kcal/mol in SCRF, respectively, which are much higher than that of **9**. These energy differences are good agreement with the experimental results (0 and 15% yields for **8** vs 80% for **2**).[4d] At the transition structure **10a-ts1** for the cyclization of the dichloro anion **10a**, the distance of the C1−C2 bond is 1.37 Å, which is only 0.02 Å longer than that of **10a**, while the distance of one of the C−Cl bonds increases by 0.15 Å. These data suggest the cyclization is promoted by chlorine atom with its leaving-group ability rather than its electronegativity. This tendency is also distinguished for the dibromo compound **10b**. One of the C−Br bonds in **10b-ts1** is 2.08 Å in length, which is longer than that of **10b** by 0.17 Å. While the order of electronegativity of the halide atoms is F ≫ Cl > Br, the order of the leaving group ability of the halide atoms is Br > Cl ≫ F. Although fluorine atoms can stabilize the negative charge well when the oxyanion attacks the π-bond, chlorine and bromine atoms can stabilize it much less effectively. Therefore chlorine and bromine atoms

(6) Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15255.

(7) 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.; Baboul, A. G.; 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.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.9; Gaussian, Inc., Pittsburgh, PA, 1998.

(8) The scale factors for B3LYP are very close to 1.0; see: Bauschlicher, C. W., Jr.; Partridge, H. *J. Chem. Phys.* **1995**, *103*, 1788−1791. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.

(9) The magnitudes of the imaginary frequency are as follows [B3LYP/6-31+G(d),SCRF(Dipole)]: −333 (**9-ts1**), −184 (**9-ts2**), −409 (**10a-ts1**), −392 (**10b-ts1**), −370 (***E*-11-ts**), −333 (***Z*-11-ts**), −402 (***E*-12-ts1**)(gas), −640 (***E*-12-ts1**), −478 (***Z*-12-ts1**), −276 (**13-ts1**).

(10) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.: Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(11) (a) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486. (b) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776.

(12) (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

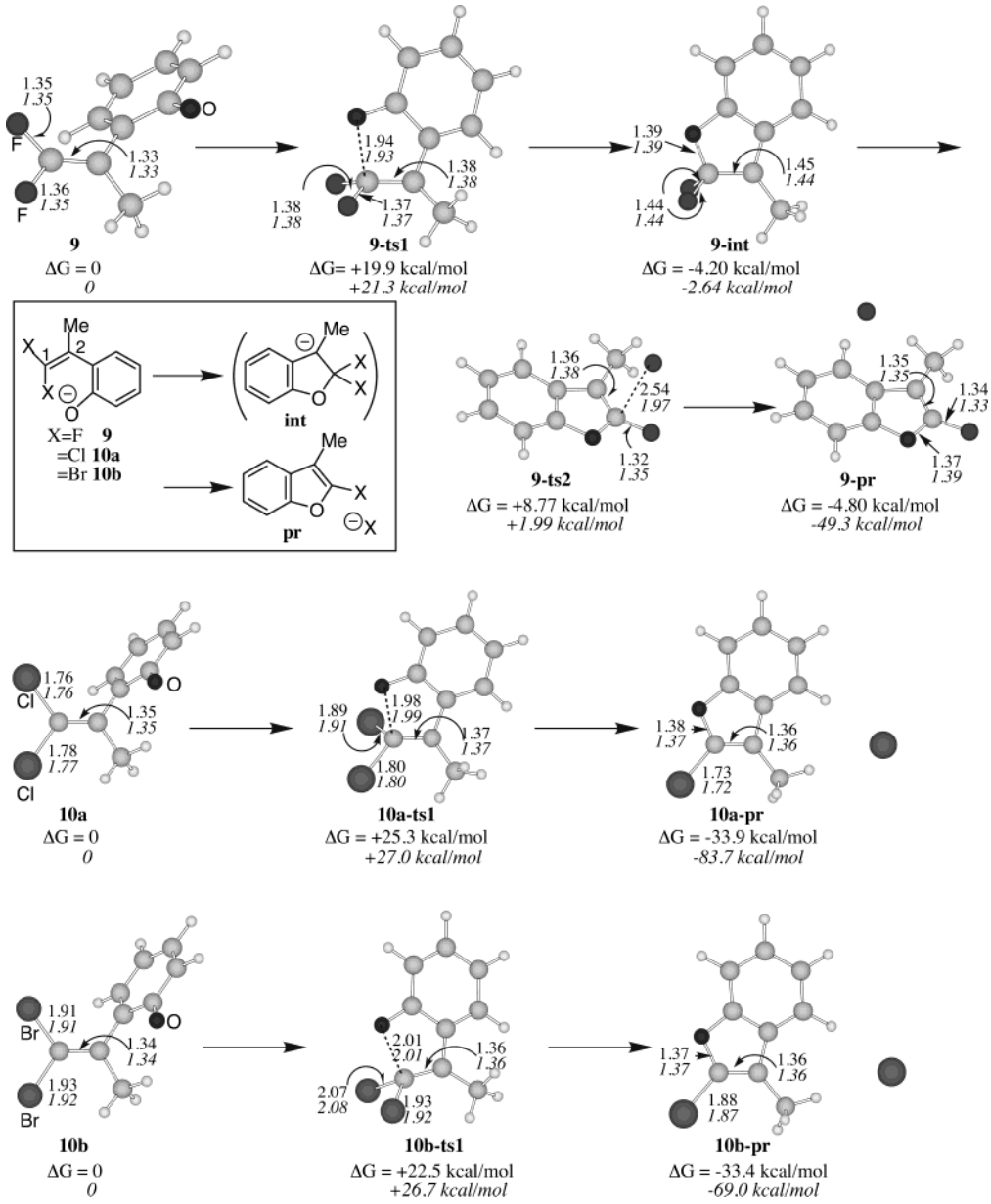


FIGURE 1. Transition structures for the nucleophilic 5-*endo-trigonal* cyclization of 1,1-dihalo-1-alkene anions **9**, **10a**, and **10b** [B3LYP/6-31+G(d)]. The italic numbers are the values in [B3LYP/6-31+G(d),SCRF(Dipole,solvent = DMF)]. Δ*G* is the relative Gibbs free energy at 298.15 K. The numbers in the structures are the bond lengths (Å).

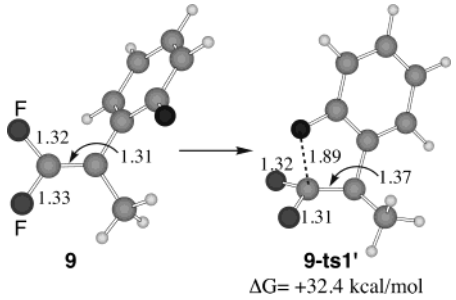


FIGURE 2. Transition structure for the cylization reaction of **9** [RHF/6-31+G(d)].

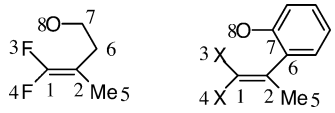
use their leaving group ability and they depart with the pair of electrons of its covalent bond. Electrostatic potential-derived charges using the CHelpG scheme of Breneman are shown in Table 1. The data for **9** in Table 1 show the C1−C2 double bond is highly polarized with the C1 positive by two fluorine atoms. On the other hand, both the C1 and C2 in **10a** are slightly positively charged. Both the reactions of **10a** and **10b** directly give two separate species, 2-halobenzo[*b*]furan and X^-, without any intermediates. It should be mentioned that both the energies and the structures of **10** and **10-ts1** in SCRF are almost the same as those in the gas phase.

We performed IRC analyses of the cyclization of **9** and **10** for deeper understanding. The IRC analyses were carried out at the B3LYP/6-31+G(d),SCRF(Dipole,DMF) level. Several representative intermediates on the IRC of **9** and **10b** are shown together with those relative energies in Figure 3. In the reaction of **9**, both the distances of the C−F bonds and C1−C2 bond increase from **9-ts1** to **A,** while the distance of the forming C−O bond decreases. Optimization starting from **A**, the last

TABLE 1. Electrostatic Potential-Derived Charges Using the CHelpG Scheme of Breneman[a]

	C1	C2	3	4	C5	C6	C7	O8
9	0.43	−0.15	F −0.25	F −0.24	0.03	0.01	0.48	−0.79
9-ts1	0.71	−0.69	F −0.34	F −0.27	0.14	0.25	0.34	−0.59
9-int	0.74	−0.64	F −0.37	F −0.37	0.13	0.24	0.18	−0.41
10a	0.09	0.12	Cl-0.17	Cl-0.19	−0.02	−0.12	0.52	−0.78
10a-ts1	0.38	−0.40	Cl-0.33	Cl-0.24	0.08	0.15	0.36	−0.53
***E*-12**	−0.06	−0.02	H 0.21	F −0.28	0.04	−0.15	0.55	−0.81
***E*-12-ts1**	0.60	−0.63	H-0.06	F−0.43	0.14	0.19	0.33	−0.61
***Z*-12**	−0.02	0.03	F −0.25	H 0.11	−0.05	0.02	0.51	−0.80
***Z*-12-ts1**	0.22	−0.54	F −0.35	H 0.09	0.07	0.29	0.36	−0.55
13	0.35	−0.06	F −0.24	F −0.23	0.00	−0.13	0.38	−1.08
13-ts1	0.74	−0.82	F −0.31	F −0.27	0.14	0.09	0.26	−0.83
13-int	1.05	−1.22	F −0.44	F −0.42	0.22	0.29	0.00	−0.47

[a] MP2/6-31+G(d). Atomic charges with hydrogens summed into heavy atoms.



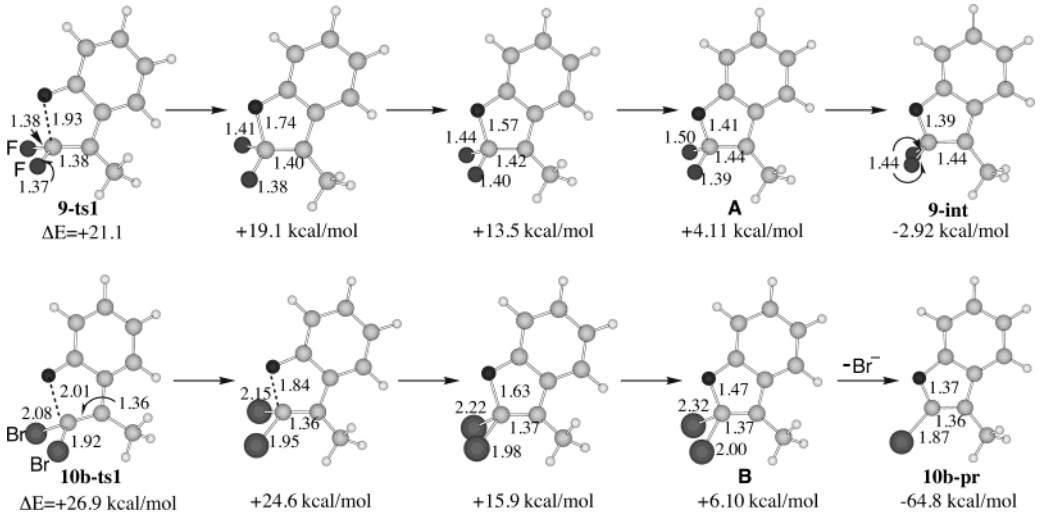


FIGURE 3. Representative intermediates on the IRC of the nucleophilic 5-*endo-trigonal* cyclization of 1,1-difluoro-1-alkene **9** and **10b** in [B3LYP/6-31+G(d),SCRF(Dipole,DMF)] together with those relative energies. The numbers in the structures are the bond lengths (Å).

structure of the IRC analysis, gave **9-int**. During the optimization, the conformational change occurs with charge re-distribution. On the other hand, the IRC analyses of the reactions of **10a** and **10b** show that only the distances of C−X (X = Cl and Br) bonds increases without changing the C1−C2 bond length when the distance of the forming C−O bond decreases (see **10b-ts1** to **B** in Figure 3). That is, the addition of oxyanion to the π-bond occurs along with the simultaneous elimination of halogen atom. Optimization starting from **B**, the last structure of the IRC analysis, gave **10b-pr** with the cleavage of the longer C−Br bond. The reaction looks like a nucleophilic substitution with retention rather than an addition−elimination one.

If the stabilization of the β-anion by fluorine atom can cooperate with a good leaving group such as bromine atom, the reaction may occur at much milder reaction conditions. We studied the cyclization reaction of the anions derived from β-bromo-β-fluoro-α-methyl-*o*-hydroxystyrenes (Figure 4). Disappointingly, the activation energies are 23.6 and 24.6 kcal/mol, close to the mean value of **9-ts1** and **10b-ts1**. This suggests the fluorine and the bromine atoms contribute to the reaction, separately. Also, there is not much difference between ***E*-** and ***Z*-11-ts**. Both the two transition structures directly gave the 2-fluorobenzo[*b*]furan and Br^-, irrespective of the olefinic stereochemistry.

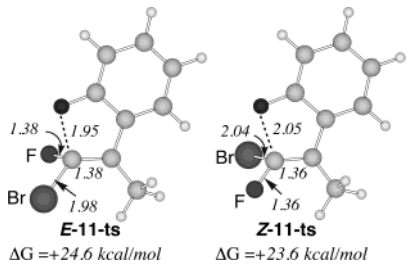


FIGURE 4. Transition structures for the nucleophilic 5-*endo-trigonal* cyclization of the anions derived from β-bromo-β-fluoro-α-methyl-*o*-hydroxystyrenes [B3LYP/6-31+G(d),SCRF(Dipole,solvent = DMF)]. ΔG is the activation Gibbs free energy at 298.15 K base on their starting structures.

The cyclization of the anions **12** derived from β-monofluoro-α-methyl-*o*-hydroxystyrenes was studied. Both the

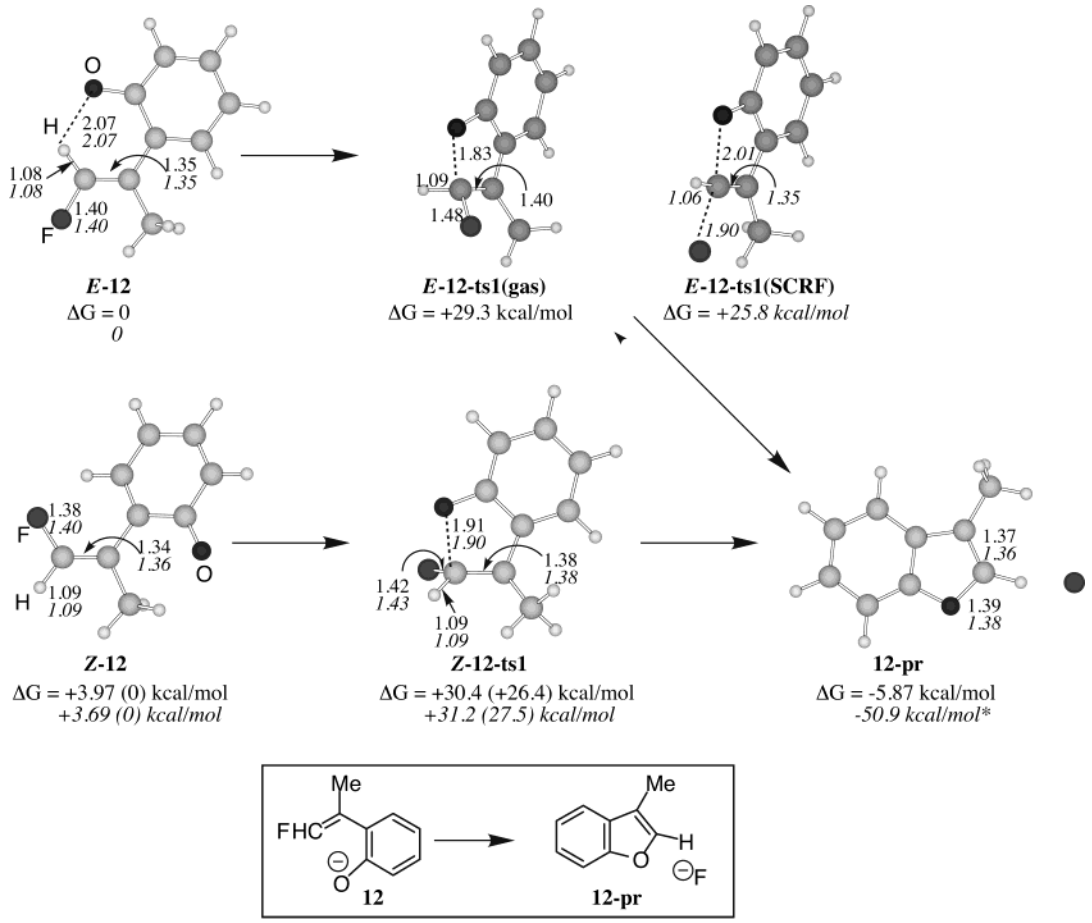


FIGURE 5. Transition structures for the nucleophilic 5-*endo-trigonal* cyclization of 1-monofluoro-1-alkenes ***E*-12** and ***Z*-12** [B3LYP/6-31+G(d)]. The italic numbers are the values in [B3LYP/6-31+G(d),SCRF(Dipole,solvent = DMF)]. Δ*G* is the relative Gibbs free energy at 298.15 K. The numbers in the structures are the bond lengths (Å).

transition structures ***E*-12-ts1** and ***Z*-12-ts1** lead to a loose complex **12-pr** in the gas phase and the two separate species **12-pr** (benzo[*b*]furan and F^-) in SCRF (Figure 5). In the gas-phase transition structure ***E*-12-ts1-(gas)**, the distance of the forming O−C bond is 1.83 Å, while the C−F and the C1−C2 bonds lengthen by 0.08 and 0.05 Å, respectively. The data suggests some delocalization of the negative charge to the carbon atom and the electronegative fluorine atom in ***E*-12-ts1(gas)**. Surprisingly, the reaction takes an S_N2 pathway with inversion at the sp^2 carbon[13] in SCRF (the dihedral angle O−C−H−F = 179.9°). A hydrogen bonding of the oxyanion with the vinylic hydrogen makes ***E*-12** a planar molecule. When the oxyanion approaches to the sp^2 carbon from a direction 180° away from the departing fluoride ion with keeping this hydrogen bonding, spontaneous dissociation of C−F bond occurs in polar solvent such as DMF. The distance of the forming O−C bond is 2.01 Å and the distance of the breaking C−F bond is 1.90 Å, while the distance of the C1−C2 bond does not change (1.35 Å). The activation energy is 25.8 kcal/mol. On the other hand, both the gas phase and the SCRF transition structures for the cyclization of ***Z*-12** are almost the same out-of-plane π-pathway with the activation energies, 26.4 and 27.5 kcal/mol. Since the hydrogen bonding is not possible for ***Z*-12**, the reaction takes an addition−elimination path. All the activation energies of ***E*-12** and ***Z*-12** are larger than that for **9** and correspondent with the experimental low yields.[4d] Thus, one vinylic fluorine atom is not sufficient to activate the alkenes for 5-*endo-trigonal* cyclization.

5-*Endo-Trigonal* Cyclization of 1,1-Difluoro-1-butenols. The above ring-formation reactions contain a benzene ring as a sp^2 carbon linker between the nucleophilic OH group and the difluoroalkene part. To see the difference between the above reaction and the cyclization of homoallyl alcohols such as **3**, the cyclization reaction of the anion **13** was studied (Figure 6). In the transition state structure **13-ts1**, the distance of the forming O−C bond is 2.06 Å in the gas phase and 1.99 Å in SCRF. While the gas-phase structures **13** and **13-ts1** are almost the same as those in SCRF, the activation energy in SCRF is bigger than that in the gas phase by 7 kcal/mol. This difference seems to come from the big stabilization of the unstable oxyanion **13** in a polar solvent compared with highly charge-delocalized **13-ts1**. In **13-ts1**, the C1−C2 bond lengthens by 0.04 Å, while C−F bonds are not much different from those in **13**. The IRC analysis was carried out at the B3LYP/6-31+G(d) level. Several representative intermediates on the IRC are shown together with those relative energies in Figure 7. From

(13) For a theoretical study on the $Cl^- + CH_2{=}CHCl$ reaction, a similar transition structure was reported: Glukhovtsev, M. N.; Pross, A.; Radom, L. *J. Am. Chem. Soc.* **1994**, *116*, 5961.

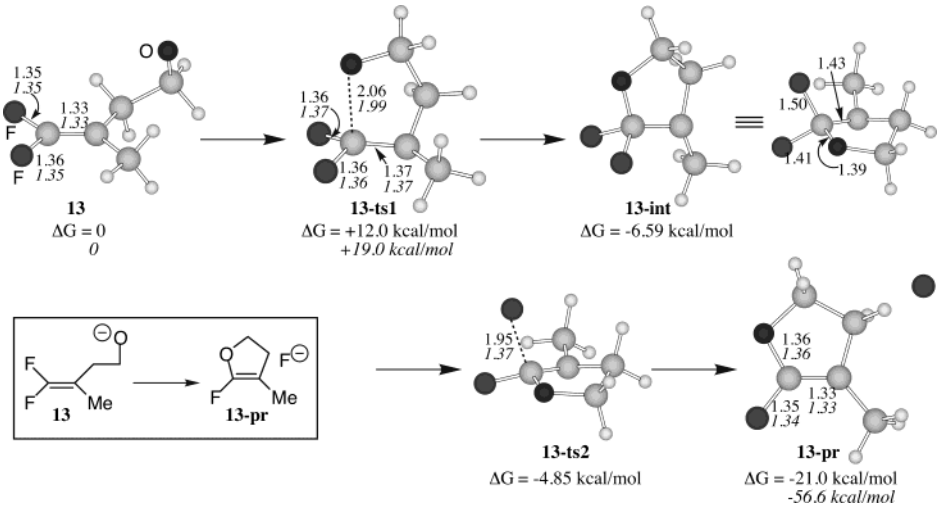


FIGURE 6. Transition structures for the nucleophilic 5-*endo-trigonal* cyclization of 1,1-difluoro-1-alkene **13** [B3LYP/6-31+G-(d)]. The italic numbers are the values in [B3LYP/6-31+G(d), SCRF(Dipole,solvent = DMF)]. Δ*G* is the relative Gibbs free energy at 298.15 K. The numbers in the structures are the bond lengths (Å).

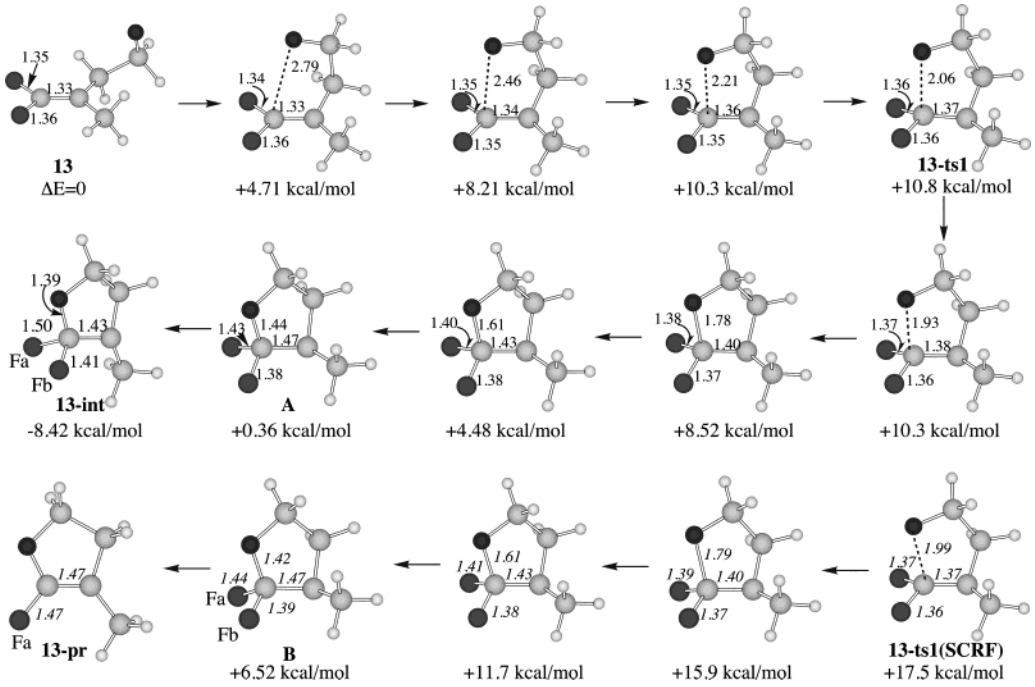


FIGURE 7. Representative intermediates on the IRC of the nucleophilic 5-*endo-trigonal* cyclization of 1,1-difluoro-1-alkene **13** [B3LYP/6-31+G(d)] together with those relative energies. The data from **13-ts1** to **13-pr** in [B3LYP/6-31+G(d),SCRF(Dipole,-DMF)] were shown in the bottom. The numbers in the structures are the bond lengths (Å).

the starting point of the reactant **13**, the energy increases with the decrease in the distance of the forming C−O bond. At the transition state (**13-ts1**), the distances of the C−O and the C1−C2 bonds are 2.06 and 1.37 Å, respectively, while other bond distances are not much different from those in **13**. After going beyond **13-ts1**, the energy decreases with both the decrease of the C−O bond length and the increase of the C1−C2 and C−F bond lengths. In the last structure **A** of the IRC analysis, the methyl group and the longer C−F bond are on opposite sides of the ring. Optimization starting from **A** gave **13-int**, in which the stereochemistry at the carbon having methyl group is inverted and the distance of the C1−C2 bond is decreased by 0.04 Å. Since the methyl group in **A** is axial and the axially substituted conformer is less stable than the equatorial one because of steric interference, the stereochemistry of the carbanion is inverted after the C−O bond formation. These data suggest the cyclization takes place by three steps, that is, the addition reaction to the π-bond, the following inversion of the carbanion stereochemistry, and the delocalization of the negative charge. Since extra stabilization of the anion intermediate by the phenyl group can be expected for **9-int**, a cleavage of the longer C−Fa bond from **13-int** occurs much easier than that from **9-int**. In fact, the activation energy is only 1.74 kcal/mol in the gas phase. In SCRF calculations, the reaction occurs in the same way. The IRC analysis in SCRF from **13-ts1** to **13-pr** is

shown in the bottom of Figure 7. The last structure **B** is almost the same as **A** in the gas phase. Optimization starting from **B** gave **13-pr** (5-fluoro-2,3-diydrofuran and F^-) without any intermediate. Interestingly, the cleavage of the shorter C−Fb bond occurs in SCRF. Careful investigation on the optimization process shows that the cleavage of the C−Fb bond occurs when the carbon having methyl group flattens after the C−O bond formation. Thus, the cyclization reaction of **13** occurs in a similar manner with **9**.

Conclusion

In conclusion, the nucleophilic 5-*endo-trigonal* cyclization of 1,1-difluoro-1-alkenes have been studied at the B3LYP/6-31+G(d) level in an Onsager continuum model for DMF. The transition structures and the IRC analysis suggest the delocalization of the negative charge in the addition intermediate to highly electronegative two fluorine atoms is the origin of the high reactivity for both **9** and **13**. Both dichloro and dibromo counterparts are much less reactive for 5-*endo-trigonal* cyclization. In these substrates, the cyclization reaction was promoted by chlorine or bromine atom with their good leaving-group ability rather than the delocalization of the negative charge. The study on the cyclization of β-monofluoro-*o*-hydroxystyrenes shows that a fluorine atom is not enough to delocalize the negative charge in the addition step. Since hydrogen bonding of the oxyanion with the vinylic hydrogen makes ***E*-12** a planar molecule, the reaction of ***E*-12** in SCRF takes a concerted in-plane σ-type S_N2 pathway with inversion at the sp^2 carbon. Further studies on S_N2 pathway with inversion at a sp^2 carbon are in progress in our laboratory.

Since beneficial effects of fluorine substitution on organic molecules are well-known, tremendous efforts to develop new methodologies for construction of fluorinated organic molecules have been made for these two decades. We believe an understanding on the reactivity of fluorinated compounds will be useful for the development of new reactions.

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Supporting Information Available: Atom coordinates of **9-ts1**, **10b-ts1**, and **13-ts1** in SCRF and both gas and SCRF ***E*-12-ts1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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