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Theoretical and Experimental Study on the In-Plane S_N2-Type Substitution Reaction of Haloalkenes with Inversion of Configuration at the sp^2 Carbon†

Kaori Ando,*,‡ Mitsuru Kitamura,§ Kasei Miura,§ and Koichi Narasaka*,§

College of Education, University of the Ryukyus, Nishihara-cho, Okinawa 903-0213, Japan, and Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

ando@edu.u-ryukyu.ac.jp

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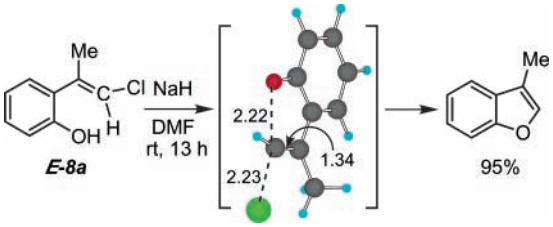
ABSTRACT



The intramolecular in-plane S_N2 type reaction of haloalkene *E*-8a was predicted to be a facile process for the first time by DFT calculations (B3LYP/6-31+G(d),SCRF(dipole, solvent = DMF)) (ΔG = 14.4 kcal/mol). The prediction was confirmed experimentally. When *E*-8a was treated with NaH in DMF, benzofuran was obtained in 95% yield. On the other hand, *Z*-8a was recovered quantitatively even after heating at 110 °C.

The bimolecular nucleophilic substitution (S_N2) reaction is one of the most fundamental reactions in organic chemistry. The S_N2 reaction at the sp^3 carbon takes place in a single step without intermediates when the entering nucleophile attacks the substrate from a position 180° away from the leaving group. On the other hand, there are a wide variety of possible mechanisms for the corresponding S_N2 reaction at the sp^2 carbon.[1] The most common route is an addition−elimination pathway, which is initiated by nucleophilic attack at the π-bond. The in-plane S_N2 route, in which the backside attack of the nucleophile occurs concertedly with leaving group expulsion within the molecular plane, has long been rejected as a feasible pathway. Recently, the in-plane S_N2 route has been predicted to be feasible on the $Cl^- + CH_2{=}$CHCl reaction by ab initio calculations.[2] Following this discovery, the in-plane S_N2 process received considerable attention.[3] However, the reported activation energies of the theoretically calculated in-plane vinylic S_N2 reactions of haloalkenes are high (more than 30 kcal/mol) and no experimental support has been provided.[2,3c] Only the reaction of vinyl iodonium salts with halide ions[1b,4] and the reactions with charged three-membered rings are known.[5]

During the course of our study on the nucleophilic cyclization of haloalkenes,[6,7] one of us found that the cyclization of fluoroalkene ***E*-1a** occurs via the in-plane S_N2

† This paper is dedicated to Professor K. N. Houk on the occasion of his 60th birthday.

‡ University of the Ryukyus.

§ The University of Tokyo.

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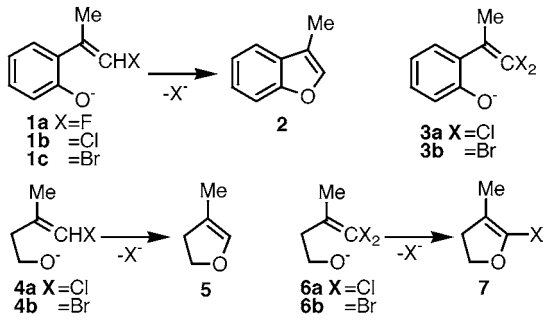
Scheme 1



pathway in an Onsager continuum model for dimethylformamide (DMF)[8] (ΔG = 25.8 kcal/mol) and occurs via a concerted π-addition−elimination pathway in the gas phase [B3LYP/6-31+G(d)] (Scheme 1).[6] This mechanistic change inspired us to do further study on the in-plane S_N2 reaction. All calculations were performed using the Gaussian 98 program.[9,10]

The transition structure for the cyclization of ***E*-1b** was located in the gas phase and in solution by the B3LYP hybrid functional[13] together with the 6-31+G(d) basis and the Onsager continuum model[14] for DMF (ϵ = 37.06) (Figure 1). The in-plane S_N2 transition structure ***E*-1b-ts** was obtained with the activation free energy of 14.4 kcal/mol in DMF (17.1 kcal/mol in the gas phase). Hydrogen bonding of the oxyanion with the vinylic hydrogen makes ***E*-1b** a planar molecule. The intrinsic reaction coordinate (IRC) calculations showed that spontaneous dissociation of the C−Cl bond occurs when the oxyanion approaches the sp^2 carbon while

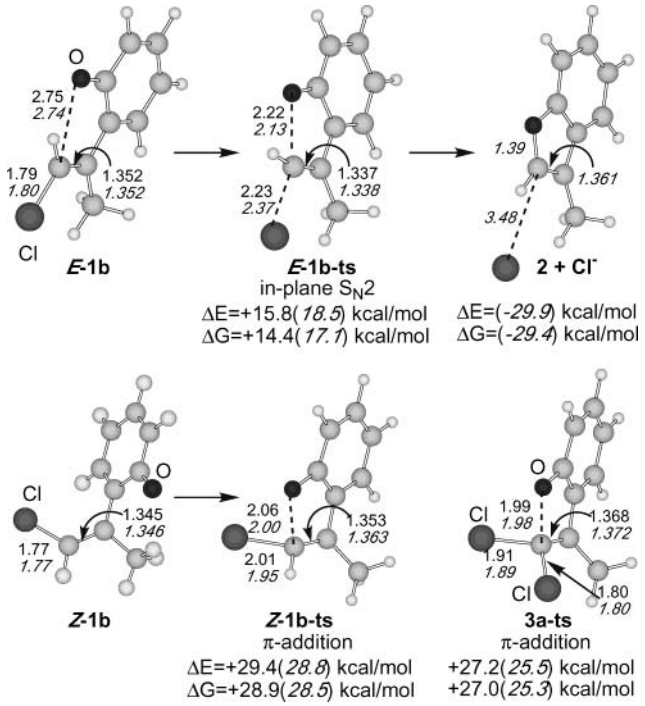


Figure 1. Transition structures for the nucleophilic cyclization of chloroalkene anions **1b** and **3a** [B3LYP/6-31+G(d), SCRF (dipole, solv = DMF)]. The italic numbers are the values in the gas phase.

keeping this hydrogen bonding (the O−H distance is 2.00−2.23 Å). The distances of the forming O−C and the breaking C−Cl bonds are 2.22 and 2.23 Å in ***E*-1b-ts**, respectively, while the distance of the C=C double bond was slightly reduced. Even after many trials, we could not get any π-addition transition structures. On the other hand, only π-addition transition structures are obtained from both ***Z*-1b** and the dichloro compound **3a**.[6] Due to both the steric hindrance and electronic repulsion between the oxyanion and the electronegative chlorine atom, both ***Z*-1b** and **3a** are no longer planar molecules and the oxyanion approaches to the sp^2 carbon to the double bond plane perpendicularly. The activation energies of these are much higher than the one of ***E*-1b**. The high activation energies for the π-addition are mainly associated with large deformation energies required to adjust the reactants to their TS geometry without interaction with the nucleophile. The deformation energy might be roughly estimated by the energy difference (38.6 kcal/mol) between ***Z*-1b** and ***Z*-1b-ts**, in both of which the alkoxy anion was replaced with a hydrogen. Since the deformation energy destabilizes the π-addition TS and the intramolecular hydrogen bonding stabilizes the in-plane S_N2 type reaction, ***E*-1b-ts** becomes the only favorable pathway. The in-plane S_N2 type reaction is also the preferred pathway for the corresponding bromoalkene ***E*-1c**.[15]

To see the effect of the benzene ring as a linker, the cyclization reaction of the anion **4a** was studied. The transition structures for the cyclization of ***E*-4a** were located

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(8) Since DMF is able to dissolve many salts and tends to surround metal cations rather than nucleopfilic anions, the use of free anions as model systems could be approved.

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(10) Gibbs free energies are the values at 298.15 K and 1.00 atm. The thermal energy corrections are not scaled.[11] Vibrational frequency calculations gave only one imaginary frequency for all transition structures and only harmonic frequencies for the reactants and products. The structures of the reactants and products were obtained by the optimization of the last structures on both sides of IRC calculations.[12]

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(15) Full details will be soon presented.

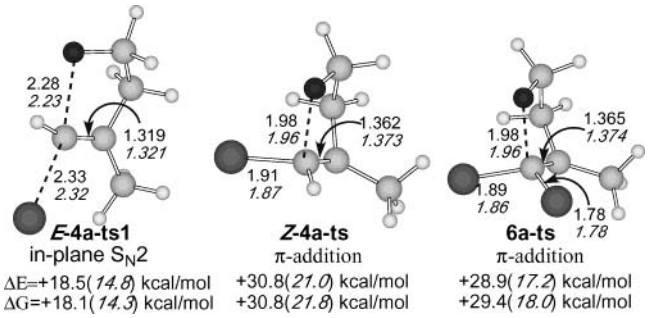
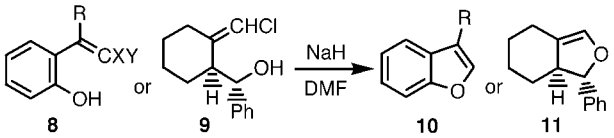


Figure 2. Transition structures for the nucleophilic cyclization of chloroalkene anions **4a** and **6a** [B3LYP/6-31+G(d), SCRF (dipole, solv = DMF)]. The italic numbers are the values in the gas phase.

(Figure 2). The in-plane S_N2 type transition structure ***E*-4a-ts1** is more stable than the π-addition transition structure ***E*-4a-ts2** (not shown) by 11.9 kcal/mol (DMF) (ΔG). Only π-addition transition structures are obtained from both ***Z*-4a** and the dichloro compound **6a**. The activation energies are much higher than the one associated with ***E*-4a-ts1**. It should be noted that the activation energies in DMF are higher than the ones in the gas phase by 4 kcal/mol for ***E*-4a-ts1** and 7−11 kcal/mol for the π-additions. These differences seem to arise from a large stabilization of the unstable oxyanions **4a** and **6a** in a polar solvent compared with their corresponding transition structures.

The theoretical predictions were confirmed experimentally, by preparing haloalkenes **8** and **9**. The *E*- and *Z*-isomers were separated by column chromatography and the geometry of the olefin moiety was determined by NOE experiments. The stereochemistry of ***E*-9** was determined by X-ray analysis. When ***E*-8a** was treated with NaH in DMF at room temperature, benzofuran **10** was obtained in 95% yield (entry 1 in Table 1). On the other hand, ***Z*-8a** was recovered quantitatively even after heating at 110 °C. In a similar way, the bromoalkene ***E*-8b** reacted smoothly to give **10** in 73% yield at room temperature. ***Z*-8b** gave **10** in only 6% yield after a prolonged reaction time (rt, 6 days) along with 87% of ***Z*-8b**. These experimental results including the previous data from the fluoroalkene ***E*-8d** (***E*-8a** is more reactive than ***E*-8d**) and **8c**[16] consist of the DFT calculations and support the in-plane S_N2 mechanism for ***E*-8**. Furthermore, **9** was

Table 1. Intramolecular Nucleophilic Substitution Reaction



8 9 10 11

entry	substrate(R, XY)	conditions	yield[b] (%)	recovery[c] (%)
1	***E*-8a** (Me, HCl)	rt, 13 h	95	
2	***Z*-8a** (Me, HCl)	rt to 110 °C[a]	0	100
3	***E*-8b** (Me, HBr)	rt, 3 h	73	
4	***Z*-8b** (Me, HBr)	rt, 6 days	6	87
5	***E*-9**	80 °C, 10h	82	
6	***Z*-9**	80 °C, 10 h	0[d]	
7	**8c** (Bu, Cl_2)	60 °C, 2h	0[e]	
8	***E*-8d** (Bu, HF)	80 °C, 43 h	17[e]	

[a] rt, 13 h; 50 °C, 1 h; 80 °C, 1 h; 110 °C, 1 h. [b] Isolated yield. [c] The recovery of the substrate. [d] A complex mixture. [e] Ref. 16.

treated with NaH in DMF at room temperature. ***E*-9** gave the S_N2 product **11** in 82% yield, while **11** was not obtained from ***Z*-9**.

In summary, we showed the first in-plane S_N2 type reaction of haloalkenes by both DFT calculations and experiments. The in-plane S_N2 pathway opens up many possibilities for mainly intramolecular reactions, from which useful methodologies in organic synthesis can be developed. Further investigation on this type of reaction is currently in progress in our laboratories.

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Supporting Information Available: Typical experimental procedure, spectral data for new compounds, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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