# Mechanism of Racemization in the Reaction of 4-Methylcyclohexylidenemethyliodonium Salt with Sulfonate Ions: Formation of Intermediate Cycloheptyne

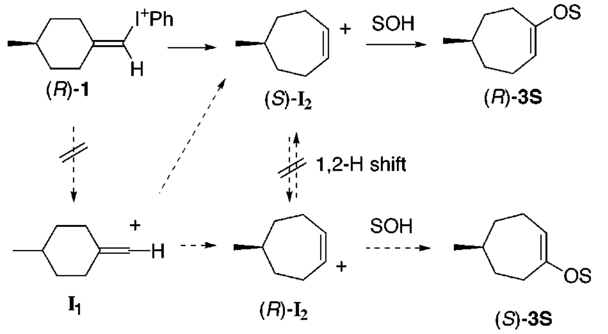
Morifumi Fujita,* Yuichi Sakanishi, and Tadashi Okuyama*

*Faculty of Science*
*Himeji Institute of Technology*
*Kamigori, Hyogo 678-1297, Japan*

*Received June 14, 2001*
*Revised Manuscript Received July 27, 2001*

In a recent paper,[1] we have established that a primary vinyl cation is not involved in the solvolysis of chiral 4-methylcyclohexylidenemethyl(phenyl)iodonium tetrafluoroborate ($\mathbf{1}\cdot BF_4^-$). That is, the solvolysis of (*R*)-**1** in various alcoholic solvents ranging from methanol to hexafluoro-2-propanol gives stereospecifically a rearranged product, (*R*)-4-methylcycloheptanone as a major product, maintaining completely the chirality of the substrate. This result excludes the intermediate formation of achiral, primary 4-methylcyclohexylidenemethyl cation ($\mathbf{I_1}$), but conforms to the concerted $\sigma$-bond participation to lead to chiral, secondary (*S*)-5-methylcyclohept-1-enyl cation ($\mathbf{I_2}$) (Scheme 1). Furthermore, the 1,2-hydride shift between (*S*)-$\mathbf{I_2}$ and (*R*)-$\mathbf{I_2}$ should not occur during the reaction.

**Scheme 1**

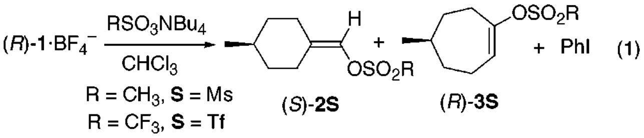


Primary vinyl cations are generally unstable and cannot be generated under normal solution conditions.[2] Some suggestions of their formation are only based on the observed rearrangement and obviously are not definitive. Hinkle and co-workers[3] have recently suggested the formation of a primary vinyl cation during the thermal reaction of 2,2-dialkylvinyl(aryl)iodonium triflates in chloroform, on the basis of observations that the products included both *E/Z* isomeric unrearranged triflates as well as rearranged ones. For comparison, we have examined the reaction of **1** under similar conditions: a tetrafluoroborate salt of (*R*)-**1** was treated with sulfonates in chloroform. The rearranged product obtained from the reaction with mesylate was largely racemized in contrast to the solvolysis results.[1] The $^{13}$C-labeling of **1** showed that the primary cation was not involved in the sulfonate reaction. The cause of these results seemed to be the hydride-shift racemization of $\mathbf{I_2}$ facilitated by the sulfonate. Further examination, however, showed that the deuterium isotope exchange does occur during the reaction, indicating that the racemization is due to intermediary formation of cycloheptyne. In this communication all of those unexpected observations will be detailed.

**Table 1.** Reaction of 69% ee of (*R*)-**1** (2.5 mM) with Tetrabutylammonium Sulfonate in Chloroform at 60 °C for 6 h

| | | yield (%) | | | ee (%) | |
|---|---|---|---|---|---|---|
| [SO$^-$] (M) | S | **2S** | **3S** (**2S**:**3S**) | PhI | (*S*)-**2S** | (*R*)-**3S** |
| 0.01 | Ms | 47 | 21 (69:31) | 95 | 67 | 7 |
| 0.05 | Ms | 55 | 21 (72:28) | 98 | 65 | 17 |
| 0.1 | Ms | 62 | 21 (75:25) | 98 | 63 | 21 |
| 0.2 | Ms | 60 | 23 (72:28) | 100 | 59 | 30 |
| 0.01 | Tf | 24 | 43 (36:64) | 96 | 56 | 55 |
| 0.05 | Tf | 21 | 54 (28:72) | 96 | 52 | 59 |
| 0.1 | Tf | 18 | 55 (25:75) | 92 | 47 | 62 |
| 0.2 | Tf | 14 | 50 (22:78) | 85 | 45 | 62 |

Reactions of (*R*)-**1** (69% ee)[1] with tetrabutylammonium mesylate and triflate were carried out in chloroform at 60 °C.[4] Products include 4-methylcyclohexylidenemethyl sulfonate **2S** and 5-methylcyclohept-1-enyl sulfonate **3S**, accompanied by iodobenzene (eq 1), as summarized in Table 1. The stereochemistries of **2S** and **3S** were determined to be *S* and *R*, respectively, by comparison with authentic samples,[5] and enantiomeric ratios of the products were determined by chiral GC. Triflate gave a large fraction of the rearranged product **3Tf**, and the optical purity was largely maintained in the *R* form. In contrast, mesylate yielded **3Ms** with a low ee (<30%). Extensive racemization occurred during the formation of **3Ms**. We will now focus our discussion on why the racemization occurs in the reaction with mesylate.



The $^{13}$C-labeling[6] at the exocyclic position of **1** ($^{13}$C-**1**) provides useful information about the mechanism of racemization (Scheme 2). The considerable scrambling of the position of labeling in the final product **3Ms** was observed as deduced from $^1$H and $^{13}$C NMR spectra (Table 2). As Scheme 2 shows, the rearrangement to the seven-membered cyclic cation $\mathbf{I_2}$ does not lead to the scrambling irrespective of involvement of the primary cation $\mathbf{I_1}$, but the scrambling occurs via 1,2-hydride shift of $\mathbf{I_2}$, which would

---

(1) Fujita, M.; Sakanishi, Y.; Okuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 8787−8788.

(2) (a) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. *Vinyl Cations*, Academic Press: New York, 1979. (b) Rappoport, Z., Stang, P. J., Eds.; *Dicoordinated Carbocations*, John Wiley & Sons: Chichester, 1997. (c) Photochemical generations: Lodder, G. In ref 2, pp 397−400. (d) Generation by nuclear decay: Fornarini, S.; Speranza, M. *Tetrahedron Lett.* **1984**, *25*, 869; *J. Am. Chem. Soc.* **1989**, *111*, 7402−7407. (e) In superacid: Hogeveen, H.; Roobeek, C. F. *Tetrahedron Lett.* **1971**, 3343−3346. (f) In concentrated sulfuric acid: Lucchini, L.; Modena, G. *J. Am. Chem. Soc.* **1990**, *112*, 6291−6296.

(3) Hinkle, R. J.; McNeil, A. J.; Thomas, Q. A.; Andrews, M. N. *J. Am. Chem. Soc.* **1999**, *121*, 7437−7438; 10668.

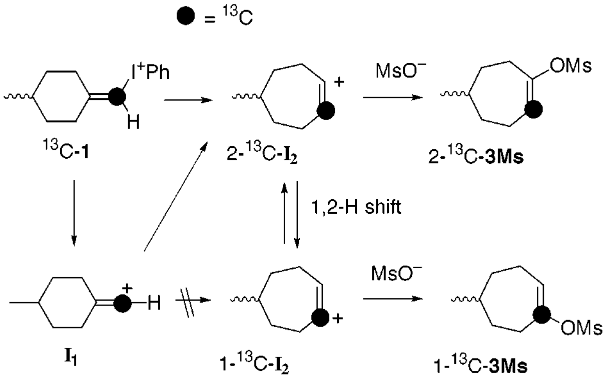
(4) The tetrafluoroborate salt of of (*R*)-**1** (1 mg) was dissolved in 1 mL of chloroform containing tetrabutylammonium sulfonates and kept at 60 °C for 6 h. The products were extracted with ether and washed with water. The yields of the products from the racemic **1** were determined by GC with tetradecane as an internal standard, while the ee of the products from (*R*)-**1** were determined using the chiral GC column.

(5) An authentic sample of optically active **2S** was prepared from (*R*)-1-dimethylphenylsilylmethylene-4-methylcyclohexane. It was converted to (*R*)-1-dimethylphenylsiloxymethylene-4-methylcyclohexane by epoxidation of the vinylsilane followed by the stereospecific rearrangement of the epoxide with $BF_3\cdot OEt_2$.[5a] Usual treatments of the optically active silyl enol ether with sulfonic anhydride[5b] gave (*R*)-**2Ms** and (*R*)-**2Tf**, which coincide with the minor enantiomer of the products **2S**, upon co-injection in the chiral GC. Acid-catalyzed hydrolysis of **3Ms** or **3Tf** gave (*R*)-4-methylcycloheptanone.[1] (a) Fleming, I.; Newton, T. W. *J. Chem. Soc. Perkin Trans. 1* **1984**, 119−123. (b) Stang, P. J.; Mangum, M. G.; Fox, D. P.; Haak, P. *J. Am. Chem. Soc.* **1974**, *96*, 4562−4569.

(6) The tetrafluoroborate of the labeled substrate $^{13}$C-**1** was prepared by the procedure used for the racemic **1**,[1] except for use of triethyl phosphonoacetate-*2-$^{13}$C* (Aldrich), and applied to the mesylate reaction. The products were chromatographically isolated and analyzed by $^1$H and $^{13}$C NMR as detailed in Supporting Information.

10.1021/ja016414p CCC: $20.00

**Scheme 2**



be coupled with racemization. The degree of racemization due to the scrambling can be calculated and translated to the ee. Table 2 shows that ee's calculated agree well with the observed values. That is, all the racemization should occur with scrambling of the 1 and 2 positions, and it does not involve the primary cation at all. If we consider the reactions in the framework of the reaction scheme of 1 or 2, interconversion between (*S*)-**I**$_2$ and (*R*)-**I**$_2$ should have occurred in some way. The 1,2-hydride shift was not observed during the solvolysis of **1**, and the barrier should be high. Can added sulfonate lower the barrier for the 1,2-hydride shift?

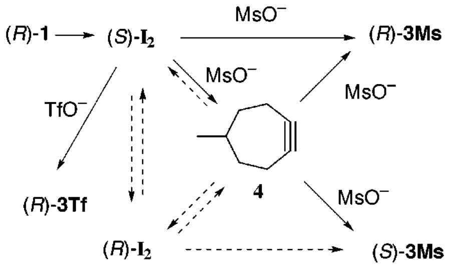
**Table 2.** Reaction of $^{13}$C-**1**·BF$_4^-$ (2.5 mM) with Tetrabutylammonium Mesylate in Chloroform at 60 °C for 4 h

| | | | ee of **3Ms** (%) | |
|---|---|---|---|---|
| [MsO$^-$] (M) | **2Ms**:**3Ms** | *A*[a] | calcd[b] | obsd[c] |
| 0.01 | 76:24 | 44/56 | 8 | 7 |
| 0.05 | 74:26 | 38/62 | 17 | 17 |
| 0.1 | 78:22 | 35/65 | 21 | 21 |
| 0.2 | 80:20 | 31/69 | 26 | 30 |

[a] *A* = 1-$^{13}$C-**3Ms**/2-$^{13}$C-**3Ms**. [b] Calculated by ee = EE(1 − *A*)/(1 + *A*), where EE is the ee of the starting iodonium salt **1** (EE = 69). [c] Observed values obtained from reation of (*R*)-**1** (69% ee), taken from Table 1.

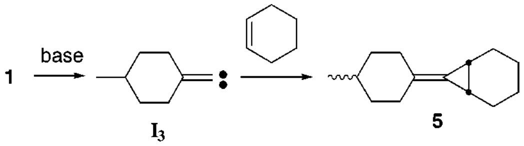
We suspected the possibility of an elimination−addition mechanism for the interconversion of the isomeric cations **I**$_2$. In fact, deuterium incorporation was observed when the reactions of **1** with sulfonates were carried out in the presence of $CH_3OD$ for the source of deuteron.[7] Elimination of an olefinic hydrogen obviously occurs, and achiral 5-methylcycloheptyne (**4**)[8] must be involved. Interconversion of the cations means reversible deprotonation/protonation, but nucleophilic reaction of **4** is also possible. The reaction with less basic triflate gives (*R*)-**3Tf** without loss of the optical purity. Competitive reactions of **1** in the presence of both mesylate and triflate were also examined. Both **3Ms** and **3Tf** were obtained: their ee's are different from each other but much the same as those of the respective products obtained independently.[9] That is, there must be at least two different intermediates to give rearranged products **3S**. One is (*S*)-**I**$_2$ which probably gives (*R*)-**3Tf** and (*R*)-**3Ms** on reaction with respective sulfonates, while the other is alkyne **4** that is formed and trapped only by mesylate, giving racemic **3Ms**, but not by triflate. The most likely pathway involves formation of (*S*)-**I**$_2$ via $\sigma$-bond participation of (*R*)-**1** followed by deprotonation with mesylate nucleophile to give the intermediate alkyne **4**. Mesylate works both as a base to give **4** and also as a nucleophile to trap **4**, but a poorly reactive triflate can only trap the cation **I**$_2$ as a nucleophile (Scheme 3).

**Scheme 3**



α-Elimination from the substrate **1** could furnish **4** via rearrangement of the initially formed 4-methylcyclohexylidenecarbene (**I**$_3$) (Scheme 4). If **I**$_3$ were formed, it would be trapped by an added alkene. However, the cyclohexene adduct could not be detected from the mesylate reaction of **1** in the presence of cyclohexene: the product distribution and ee were not affected by added alkene. In a control experiment, **I**$_3$ was generated by the reaction of **1** with triethylamine in the presence of cyclohexene to afford the cyclopropane product in 76% yield (Scheme 4).[10] The rearrangement of **I**$_3$ does not readily occur. These experiments rule out the possibility of the carbene route for racemization.

**Scheme 4**



In conclusion, racemization of optically active vinyl iodonium salt **1** observed in the reaction with sulfonates is rationalized by intermediate formation of cycloheptyne **4**, but the primary vinyl cation **I**$_1$ is not involved in this reaction. The transient cycloheptyne **4** must be generated by deprotonation of the cation **I**$_2$ formed via concerted $\sigma$-bond participation in heterolysis of **1**.

**Supporting Information Available:** Detailed experimental procedures (PDF). This material is available free charge via the Internet at http://pubs.acs.org.

JA016414P

---

[7] The mesylate reaction of racemic **1**·BF$_4^-$ was carried out in $CHCl_3$ containing 1% of $CH_3OD$ at 60 °C. The isolated products were analyzed by $^1$H NMR. The **3Ms** contained 71% D at the olefinic position, while the **2Ms** did not contain any of D.

[8] Cycloheptyne is known as a transient species. For reviews, see: Sanders, W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1455−1456. Krebs, A.; Wilke, J. *Top. Curr. Chem.* **1983**, *109*, 189−233.

[9] Competitive reaction of **1** was performed in the presence of both tetrabutylammonium mesylate and triflate using (*S*)-**1**·BF$_4^-$ as the substrate. The results are given in Table S1 (Supporting Information).

[10] The reaction of **1**·BF$_4^-$ with triethylamine was carried out in the presence of 10 equiv of cyclohexene to give a diastereoisomeric mixture of the cyclopropane product **5** in 76% yield. The mesylate reaction was also carried out in the presence of cyclohexene, but no **5** was detected.