

Review

Chirality probe approach to reactive intermediates

Primary vinyl cation and cycloalkyne

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Abstract: Molecular chirality of 4-methylcyclohexylidenemethyl iodonium salt is used to probe the chirality of intermediate state of the reaction. A possible achiral intermediate, primary vinyl cation is excluded for the reactions of the iodonium salt under any reaction conditions employed, while achiral 5-methylcycloheptyne, formed via rearranged cation, is involved in the reaction with sulfonate. The reaction is extended to generation of some small ring cycloalkynes. Vinylic S_N2 mechanisms are also proposed.

Key words: Vinyl cation; cycloalkyne; vinyliodonium salt; molecular chirality; vinylic S_N2 reaction.

Introduction. It is usually quite difficult to definitely prove intermediacy of an unstable species in the course of reaction. One of such elusive organic intermediates is primary vinyl cation, and it arouses still controversy on its existence in solution.^{1,2)} Gas-phase stabilities of vinyl cations were evaluated both experimentally and theoretically,³⁾ and primary vinyl cations, $>C=C^+H$, were found to be thermochemically very unstable. The more stable structure of parent vinyl cation is a non-clas-



Classical vinyl cation



Bridged form

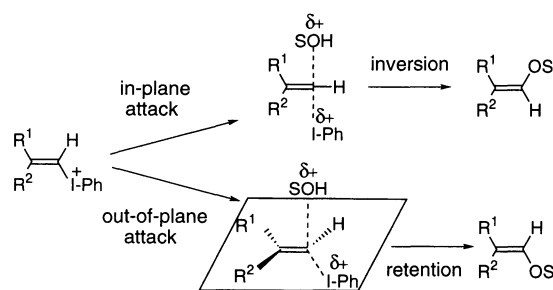
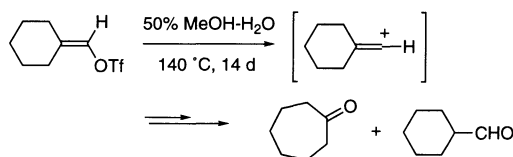
sical bridged form rather than a classical linear form.³⁾

Primary vinyl cations are also kinetically labile in solution, and they were only observed under very special conditions such as in strong acid,⁴⁾ under photo-irradiation,⁵⁾ and by nuclear decay.⁶⁾ However, no structural information is available in solution. Solvolysis of vinyl substrates are considered to proceed usually via a vinyl cation intermediate.⁷⁾ Earlier work uses alkenyl triflates (trifluoromethanesulfonates) as good substrates.⁸⁾ We have recently used alkenyl(aryl)iodonium salts with a

still better nucleofuge, iodoarene, the leaving ability of which is about 10^6 times better than triflate.⁹⁾ Although extensive rearrangements have been observed during the reactions of 2-phenylvinyl^{10)-12a)} and 2,2-dialkylvinyl iodonium salts,^{12),13)} no definite evidence for simple heterolysis to give a primary vinyl cation was found even in non-nucleophilic polar solvents like 2,2,2-trifluoroethanol (TFE). Un-rearranged substitution products were also obtained from the iodonium salts, and the *E/Z* isomeric ratios of these products were initially argued for suggesting formation of primary vinyl cation.^{12),13)} However, this suggestion was later disregarded.^{12c),14)} They could be more reasonably accounted for by the vinylic S_N2 reactions via both in-plane σ^* and perpendicular π^* attacks (Scheme 1).^{15),16)} The confusions arise from the diversity of possible interpretations of these experimental observations.

Alkenediazonium salts are also good precursors for vinyl cations. Their reactions usually result in formation of rearranged products, but no definite evidence was provided for primary vinyl cation intermediate.¹⁷⁾ On the other hand, Hanack and co-workers¹⁸⁾ suggested that solvolysis of cyclohexylidenemethyl triflate took place via the primary vinyl cation in aqueous methanol (Scheme 2). The solvolysis in 50% aqueous methanol afforded rearranged cycloheptanone and un-rearranged cyclohexanecarbaldehyde at 140 °C in 2 weeks, but no reac-

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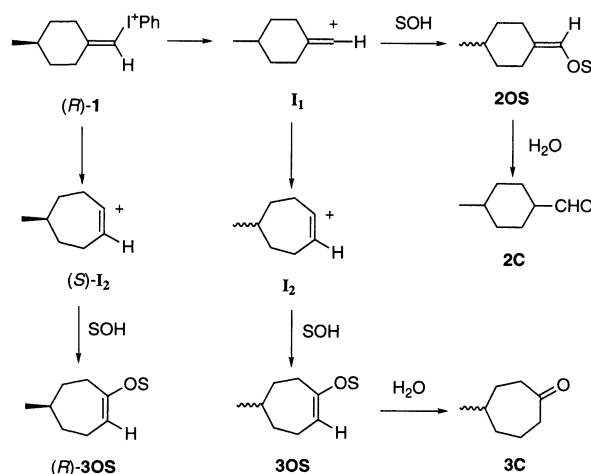
Scheme 1. Vinyllic S_N2 mechanisms

Scheme 2

tion occurred in less polar, pure methanol. However, these observations have much ambiguity because the rearrangement can occur not only via primary vinyl cation but also through the σ -bond participation, and the un-rearranged products may be derived from the bimolecular nucleophilic substitution¹⁵⁾ as well as trapping of a possible primary vinyl cation.

We wanted to make more definite observation to show whether or not the primary vinyl cation is involved in the reaction. We consider that the most suitable substrate for this purpose is a chiral 4-substituted cyclohexylidenemethyl derivative. If the achiral, linear vinyl cation is formed from the optically active starting material, the chirality should be lost, leading to completely racemized products. In contrast, if the rearrangement occurs via the σ -bond participation, the optical purity of the substrate would be maintained throughout the reaction via the chiral secondary vinyl cation as illustrated in Scheme 3. Recent results emerged from our work based on this strategy will be summarized in this account.

Evidence against primary vinyl cation. Optically active 4-methylcyclohexylidenemethyl(phenyl)-iodonium tetrafluoroborates (**1**·BF₄[−]) were prepared and solvolysis of both of the enantiomers (*R*)- and (*S*)-**1** was examined in various solvents at 60 °C.¹⁴⁾ Products include those of substitution of both un-rearranged **2OS** and rearranged form **3OS** and their hydrolysis carbonyl products, **2C** and **3C**, as well as accompanying iodobenzene. Typical results are summarized in Table I. The main product is 4-methylcycloheptanone (**3C**)



Scheme 3

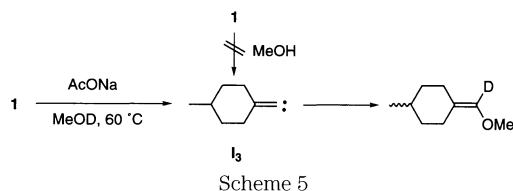
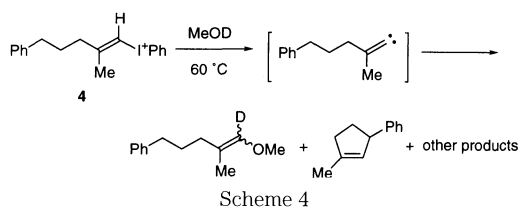
Table I. Products of solvolysis of (*R*)-**1** of 69% ee at 60 °C

Solvent ^{a)}	Time(h)	Product yield(%)			% ee	
		2OS	3C	PhI	2OS	(<i>R</i>)- 3C
EtOH	6	31	60	78	5 ^{b)}	67
MeOH	6	15	57	86	8 ^{b)}	68
(1/1) MeOH-H ₂ O	7	11 ^{c)}	80	79	—	68
TFE	9	0	75	84	—	69
HFIP	20	0	41	60	—	69
AcOH	4	15	68 ^{d)}	100	50 ^{e)}	69 ^{d)}

^{a)} TFE = 2,2,2-trifluoroethanol, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. ^{b)} Absolute stereochemistry was not determined. ^{c)} **2C**. ^{d)} **3OAc**. ^{e)} (*R*)-**2OAc**.

and/or the enol derivative **3OS**. The enol ether **3OR** is very labile to aqueous treatments, and the yield and ee (enantiomeric excess) were usually determined as **3C**. Starting with (*R*)-**1** of 69% ee, the rearranged product **3** (**3OS** or **3C**) always maintains the optical purity of the starting **1**. This result indicates the chirality of the substrate is completely transferred to the product and the structure of **3** conforms with that expected for rearrangement with σ -bond participation keeping the chirality throughout the reaction; (*R*)-**1** \rightarrow (*S*)-**I**₂ \rightarrow (*R*)-**3OS** \rightarrow (*R*)-**3C**. The enantiomer (*S*)-**1** of 79% ee gave the counterpart results. That is, primary vinyl cation **I**₁ is not involved in the course of the reaction or racemization of **I**₂ cannot occur during the reaction. Similar results were also obtained for solvolysis of a chiral vinyl tri-flate.¹⁵⁾

Racemization of **I**₂ is in principle possible via 1,2-hydride shift. This reaction of linear secondary vinyl cation easily occurs,¹³⁾ but it is theoretically rationalized that the barrier for the 1,2-hydride shift within the



cyclic vinyl cation is quite high compared to the acyclic analog.¹⁴⁾ The transition structure for the hydride shift looks like a protonated alkyne and the cyclic structure has a large angle strain.¹⁴⁾

Alkylidenecarbene intermediate. In contrast to the rearranged product, the un-rearranged product **2** loses largely the optical purity of the substrate, but it is unlikely that **2** is formed by nucleophilic trapping of the primary cation **I**₁. Cation **I**₁ should rearrange to racemic **I**₂ without any barrier, if it were formed. The vinyliodonium salt undergoes easily α elimination. Even in neutral methanol, a considerable amount of methanolysis products of a 2,2-dialkylvinyl iodonium salt **4** come from the α elimination-solvent insertion route (Scheme 4).¹³⁾

This possibility was examined, but deuterium incorporation was not observed in **2OMe** from neutral methanolysis of **1** in methanol-*d*. The methanolysis of **1** in the presence of acetate base gave exclusively **2OMe** of complete racemization, which is deuterated in MeOD. This reaction is rationalized by a mechanism involving carbene **I**₃ formed via α elimination (Scheme 5), but the α elimination pathway is excluded from neutral methanolysis. The carbene intermediacy was also confirmed by trapping with cyclohexene to give an alkylidenecyclopropane adduct under basic conditions but not under neutral conditions.

Vinyl S_N2 reactions via σ^* and π^* attack. Un-rearranged products are further examined to find a mechanism for the formation. If **I**₁ were formed, it would be trapped also by added nucleophiles in competition with nucleophilic solvent. In the presence of tetrabutylammonium bromide, **1** gave the bromide substitution product **2Br** of about 90% inversion in methanol in addition to the methanolysis products (Scheme 6).

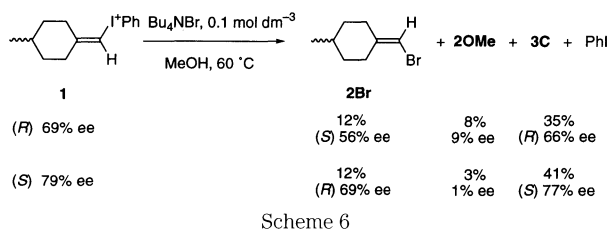


Table II. Stereochemistry of nucleophilic substitution of **1**^{a)}

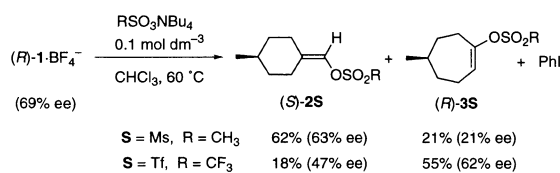
Solvent	Nucleophile ^{b)}	Inversion/Retention
AcOH	AcOH	14/86
MeOH	MeOH	54/46 or 46/54 ^{c)}
MeOH	Br ⁻	91/9
CHCl ₃	Br ⁻	92/8
CHCl ₃	AcO ⁻	54/46
CHCl ₃	CF ₃ CO ₂ ⁻	78/22
CHCl ₃	MeSO ₃ ⁻	96/4
CHCl ₃	CF ₃ SO ₃ ⁻	84/16

^{a)} Reactions were carried out at 60 °C, and ratios of inversion/retention are those of un-rearranged products **2**. ^{b)} Nucleophiles are solvent or ammonium salts at 0.1 mol dm⁻³. ^{c)} Stereochemistry of **2OMe** was not determined.

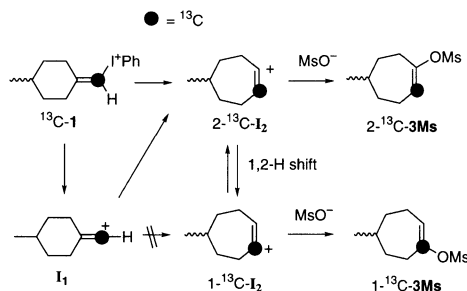
Completely different ee's of the two substitution products **2Br** and **2OMe** show that they are not formed from a common intermediate. That is, primary vinyl cation **I**₁ cannot be such an intermediate. They must be independently produced probably by direct nucleophilic substitutions of substrate **1**.

This kind of stereoselectivity of the reaction could be examined using the *E/Z* isomers of the vinyl substrates,^{12),13)} but there is a big disadvantage due to the difference in the two β substituents: the *E* and *Z* isomers do not necessarily give the same inversion/retention ratio. We do not need to worry about this problem by using chirality as a probe and calculating the stereoselectivity from the product ee.

Stereoselectivities in the reactions of **1** with various nucleophiles are summarized in Table II. Ratios of inversion/retention of configuration in formation of the un-rearranged product **2** range from mostly inversion (MeSO₃⁻ and Br⁻ in CHCl₃) to mainly retention (acetoxylation). In order to accommodate all those results, mechanisms involving concurrent S_N2 reactions via in-plane (σ^*) and out-of-plane (π^*) attack (Scheme 1) are most reasonable,¹⁶⁾ but those involving inversion plus racemization are not satisfactory. A mechanism for substitution with retention can also be rationalized as a ligand coupling within the λ^3 -iodane intermediate in the reaction of the iodonium salt.^{16c)}



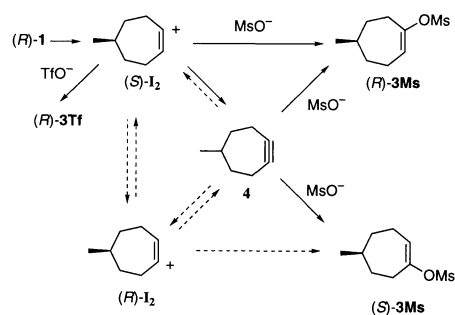
Scheme 7



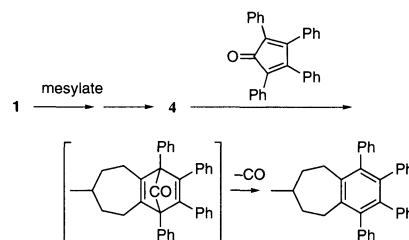
Scheme 8

Formation of cycloheptyne. Reactions of **1** with weakest nucleophiles, sulfonates in chloroform gave both un-rearranged and rearranged products as expected.¹⁹⁾ What was unexpected under those weakly nucleophilic conditions is that the rearranged product loses largely the optical purity of the substrate in the reaction with mesylate (methanesulfonate) (Scheme 7). The stereoselectivity of reaction with triflate (trifluoromethanesulfonate) is quite different from that with mesylate.

The loss of the chirality during the reaction can occur either before or after the ring expansion. This can be probed with ¹³C labeling at the exocyclic position of **1** (¹³C-**1**) (Scheme 8). The label should remain at the 2 position of the cycloheptene product, unless the racemization occurs after the rearrangement, regardless of the mechanism of rearrangement, via σ -bond participation, the primary cation intermediate **I**₁, or the alkylidenecarbene intermediate **I**₃ (not shown). However, the considerable scrambling of the position of labeling in the final product **3Ms** was observed, 1-¹³C-**3Ms**/2-¹³C-**3Ms** being about 4/6. The scrambling can occur via interconversion of **I**₂, which is coupled with racemization of the optically active substrate. The degree of racemization due to the scrambling can be calculated and translated to the ee if the reaction was started with the optically active substrate. The calculated values agree well with those obtained from (*R*)-**1** under the same conditions of varying mesylate concentrations. This indicates that all the racemization occurs with scrambling of the 1 and 2 positions, and it does not



Scheme 9

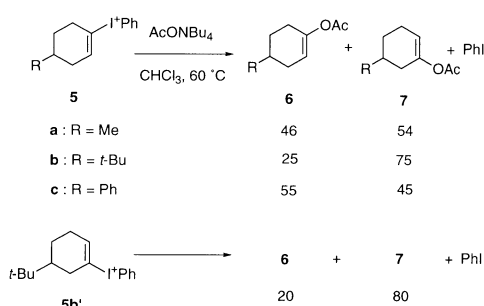


Scheme 10

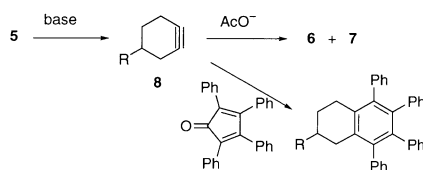
involve the primary cation **I**₁ or carbene **I**₃.

How does this scrambling occur? The barrier for the 1,2-hydride shift should be high and does not occur during solvolysis. An alternative possibility is an elimination-addition mechanism for the interconversion of the isomeric cations **I**₂. In fact, deuterium incorporation was observed when the reaction of **1** with mesylate was carried out in the presence of CH₃OD (1%) in chloroform. Elimination of an olefinic hydrogen obviously takes place to give achiral 5-methylcycloheptyne (**4**) as an intermediate (Scheme 9). Tetraphenylcyclopentadienone successfully traps the cycloheptyne in the mesylate reaction (Scheme 10).

Intermediate formation of the cycloheptyne **4** is now demonstrated, and interconversion of the cations means reversible deprotonation-protonation. However, the re-protonation of **4** is questionable, since cycloalkynes have considerable electrophilic reactivity.²⁰⁾ That is, **4** may be trapped by nucleophilic mesylate. The reaction of (*R*)-**1** 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 give both **3Ms** and **3Tf**; their ee's are different from each other but much the same as those of the respective products obtained independently. These results show that there are at least two different intermediates to give rearranged products **3Tf** and **3Ms**. One is the rearranged cation (*S*)-**I**₂, formed by σ -bond participation,



Scheme 11



Scheme 12

which gives (*R*)-**3Ms** and (*R*)-**3Tf** on reaction with respective sulfonates, while the other is alkyne **4** that can be formed and trapped only by mesylate, giving racemic **3Ms**, but not by triflate. Mesylate works both as a base to give **4** and also as a nucleophile to trap **4**, but poorly reactive triflate can only trap cation **I₂** as a nucleophile (Scheme 9). Re-protonation of **4** to revert to **I₂** is unlikely.

Further interesting observations to support the mechanisms outlined in Scheme 9 are: when the trapping experiments were carried out with the cyclopentadienone, a few percent of mesylate product **3Ms** was still formed and the survived **3Ms** maintained optical purity of the starting **1**. Optically active **3Ms** that survived cycloheptyne trapping must be formed directly from (*S*)-**I₂**, while racemized **3Ms** is formed via **4**.

Cycloheptyne and other small ring cycloalkynes have a considerable amount of strain, and can only transiently be generated in solution. For those generations, strongly basic conditions for elimination of halo-cycloalkenes are employed or some exotic precursors are devised.²⁰⁾ In view of ready formation of **4** from a vinyl cation intermediate with a mild base, we thought that this strategy could be applied to generation of other cycloalkynes.²¹⁾

Generation of cyclohexyne. Since we knew that solvolysis of 1-cyclohexenyl(phenyl)iodonium tetrafluoroborate **5** takes place via cyclohexenyl cation,⁹⁾ it was subjected to reaction with tetrabutylammonium acetate in chloroform at 60°C .²²⁾ Products are two cyclohexenyl

acetate **6** and **7** as well as iodobenzene (Scheme 11). These regio-isomeric products are best accounted for by intermediate formation of cyclohexyne **8**. This is substantiated with a similar ratio of isomeric products from the regio-isomeric iodonium salts, **5b** and **5b'**. Other bases like fluoride and triethylamine also provide cyclohexyne **8**, which is effectively trapped by the cyclopentadienone (Scheme 12).

It should be noted here that 4-*t*-butylcyclohexyne (**8b**) shows selectivity in reaction with a nucleophile in favor of the 2 position compared to poor selectivity of the methyl and phenyl analogs.

Conclusion. The chirality probe approach could definitely disprove intermediary formation of primary vinyl cation in normal solution reactions. Primary vinyl iodonium salts undergo nucleophilic reaction either by external nucleophiles or by internal nucleophilic participation from the anti-periplanar β group to avoid unstable primary vinyl cation. The participation becomes apparent only when the external nucleophile is too weak, and leads to rearrangement. Basic reaction is also possible and alkyne can be yielded if a delicate balance between nucleophilic and basic reactivities of added nucleophile/base favors deprotonation. Small ring cycloalkynes undergo immediate reaction with nucleophile.

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