

Advances in Physical Organic Chemistry

Volume 37

Edited by

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Editor's preface

Physical Organic Chemistry is a mature discipline that is blessed with a rich history and a bright future. It is therefore fitting that the chapters in this 37th volume of *Advances in Physical Organic Chemistry* deal with investigations that can be traced back to the birth of the field, but which are continuing to produce results critical to our understanding of the stability of organic molecules and the mechanisms for their reactions.

Three chapters in this volume deal with various aspects of the stability of carbocations, and their role as putative intermediates in chemical and enzymatic reactions.

Aboud, Alkorta, Dávalos and Müller summarize the results of recent experimental work to determine the thermodynamic gas phase stabilities of carbocations relative to neutral precursors, the results of high level calculations of these stabilities and additional structural information that can only be easily obtained through such calculations. The chapter concludes with a description of the effect of solvent on the condensed-phase stability of carbocations, and the role of solvent in determining whether carbocations form as intermediates of solution reactions. This chapter is richly referenced and can be read with interest by anyone wishing to remain abreast of modern developments in a historically important subject.

The generation and characterization of vinyl carbocations remains a challenging problem because of the great instability of positive charge at sp hybridized carbon. Physical organic chemists have classically produced unstable carbocations through heterolytic cleavage of bonds to weakly basic atoms or molecules. The past success of this approach has prompted the experimental studies of vinyl(aryl)iodonium salts described in the chapter by Okuyama and Lodder. Although these salts are good electrophiles that carry an excellent iodoarene nucleofuge, photoexcitation to the excited state is required to drive heterolytic cleavage to form simple primary vinyl carbocations. This chapter describes the great diversity in the products obtained from the thermal and photochemical chemical reactions of vinyl(aryl)iodonium salts and the reasoning used in moving from these product yields to detailed conclusions about the mechanisms for their formation.

Oxocarbenium ions are commonly written as intermediates of organic reactions. However, the lifetimes of oxocarbenium ions in water approach the vibrational limit and their formation as reaction intermediates in this medium is sometimes avoided through a concerted mechanism. The determination of whether oxocarbenium ions form as intermediates in related enzymatic processes is a particularly challenging problem, because the protein catalyst will shield these ions from interactions with solvent and solutes which might provide evidence for their formation. Deuterium, tritium, and heavy atom kinetic isotope effects provide a wealth of information about reaction mechanism, but these are sometimes masked for enzymatic reactions by the high efficiency for turnover of enzyme-bound substrates. However, it is often possible for creative enzymologists to develop substrates or reaction conditions under which the rate constants for enzymatic reactions are limited by chemical bond cleavage, and are therefore subject to significant kinetic isotope effects. The design and interpretation of such multiple kinetic isotope effect studies to probe the changes in chemical bonding at sugar substrates that occur on proceeding to the transition states for enzyme-catalyzed cleavage of glycosides is described in a chapter by Berti and Tanaka.

Organometallic chemistry has largely been the domain of synthetic organic and inorganic chemists, and the mechanisms for organometallic transformations have not generally been subject to the same type of detailed experimental analyses developed in studies on the mechanism of multistep organic reactions. Claude Bernasconi, a leading figure in the study of organic reaction mechanisms, summarizes here the results of studies on the reactions of organometallic Fischer carbene complexes in aqueous solution. Finally, Drechsler and Rotello describe how the redox properties of flavins, quinones and related molecules can be varied through the rational design of molecules in which a given oxidation state is stabilized by electrostatic, hydrogen-bonding, π -stacking and other noncovalent interactions. The design and physical characterization of these finely tuned redox systems has potential applications in the development of a variety of molecular "devices".

We are pleased to note that the masthead lists a revamped and expanded Editorial Advisory Board. This board is assisting the coeditors in the planning of future volumes in order to ensure that *Advances in Physical Organic Chemistry* continues to highlight the most important applications of physical and theoretical methods to the characterization of the structure and stability of organic molecules and the mechanisms for their reactions.

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Nucleophilic Vinylic Substitution and Vinyl Cation Intermediates in the Reactions of Vinyl Iodonium Salts

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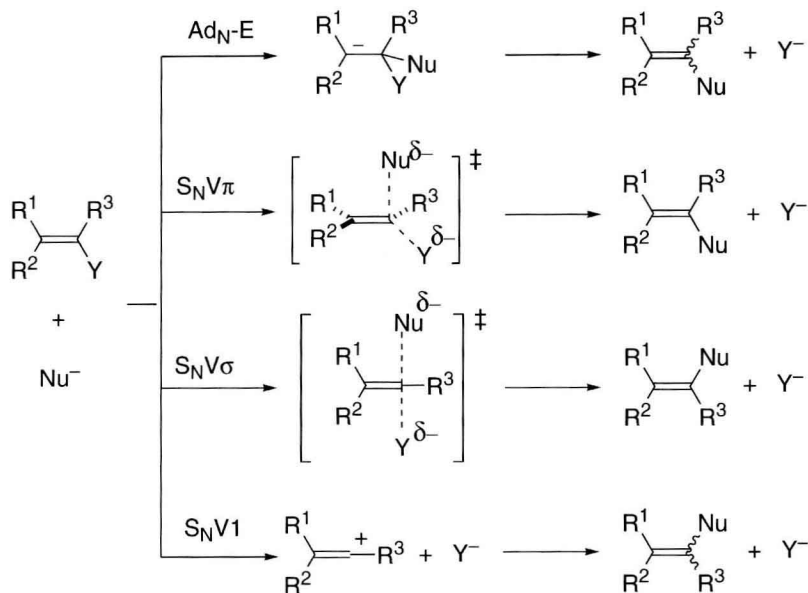
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1 Introduction

Nucleophilic vinylic substitution (S_NV) has a wide variety of mechanistic possibilities, including more than 10 main routes which can be further sub-divided into over 30 variants, as reviewed by Rappoport.¹ Four main straightforward mechanisms are illustrated in Scheme 1.

Nucleophilic attack at the alkene carbon can in principle occur either toward the π* or σ* orbitals since the sp²-hybridized carbon has two types of vacant orbitals. That is, both out-of-plane (perpendicular) and in-plane attack are possible. The out-of-plane mode of attack is part of the addition–elimination pathway (Ad_N–E) with a



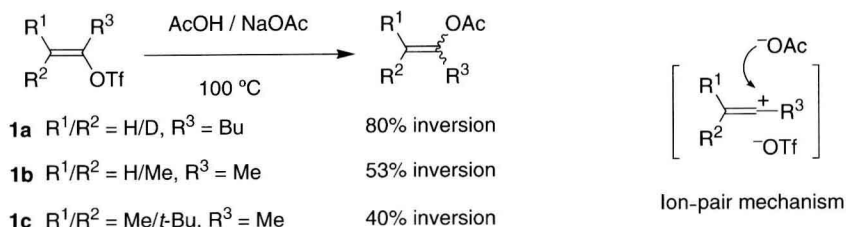
Scheme 1 Mechanisms of nucleophilic vinylic substitution.

carbanion as an intermediate. This associative mechanism is generally observed for activated unsaturated systems¹⁻³ and gives rise to products with stereochemistry ranging from retention to stereoconvergence depending on the (in)stability of the intermediate carbanions.

As the leaving group ability of Y⁻ increases, it ultimately departs concurrently with the nucleophilic attack and the reaction occurs via a "concerted addition-elimination" mechanism.¹⁻³ This type of mechanism should result in retention of configuration and may be designated as S_NVπ. In contrast, the in-plane σ* attack of a nucleophile should lead to substitution with inversion of configuration and may be referred to as S_NVσ.

With further increasing leaving ability of Y⁻, the reaction becomes dissociative and becomes a vinylic S_N1 (S_NV1) reaction involving a vinyl cation as intermediate. S_NV1 reactions have been extensively studied, both with substrates giving stabilized vinyl cations and/or with substrates with a good nucleofuge such as triflate (trifluoromethanesulfonate, TfO⁻) and are the subjects of several reviews.⁴⁻⁶ Their stereochemical consequences are discussed in Section 2.

The S_NVσ mechanism is a logical analogue of the S_N2 reaction at saturated carbon that occurs via backside attack of the nucleophile, but it has long been rejected as a feasible pathway on the basis of steric considerations^{7,8} and of early theoretical calculations on a rather crude model system.⁹ However, quite recently definite examples of S_NVσ reactions have been found,^{10,11} and recent theoretical studies¹²⁻¹⁶ show that the S_NVσ as well as the S_NVπ mechanism is feasible. If imbalance of bond formation and bond cleavage occurs, the dissociative extreme of

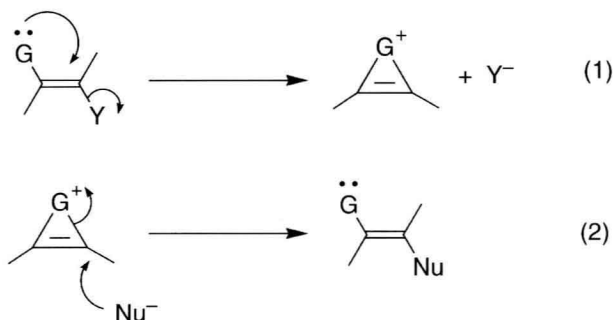
**Scheme 2**

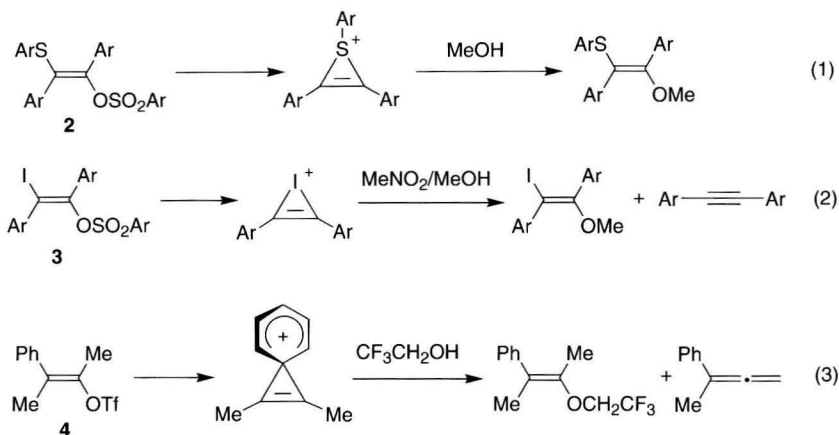
the in-plane $\text{S}_{\text{N}}\text{V}\sigma$ mechanism is formation of a vinyl cation ($\text{S}_{\text{N}}\text{V1}$ mechanism) and the associative extreme of the out-of-plane $\text{S}_{\text{N}}\text{V}\pi$ mechanism is the $\text{Ad}_{\text{N}}\text{-E}$ route. The reviews of Rappoport¹⁻³ mainly concern the associative to concerted part, $\text{Ad}_{\text{N}}\text{-E}/\text{S}_{\text{N}}\text{V}\pi$, of the mechanistic spectrum of nucleophilic vinylic substitution. In this chapter we discuss the concerted-dissociative part ($\text{S}_{\text{N}}\text{V}\sigma/\text{S}_{\text{N}}\text{V1}$ dichotomy) of the mechanistic spectrum, mainly on the basis of our recent results obtained in the study of reactions of vinyl iodonium salts. Also, photochemical dissociative reactions generating vinyl cations are discussed and compared with the corresponding thermal reactions.

2 Vinylic $\text{S}_{\text{N}}2$ reactions

$\text{S}_{\text{N}}\text{V}$ REACTIONS WITH INVERSION

The stereochemistry of nucleophilic vinylic substitution via the $\text{Ad}_{\text{N}}\text{-E}$ mechanism ranges from retention of configuration to stereoconvergence. For $\text{S}_{\text{N}}\text{V1}$ -type reactions, often partial inversion has been observed. The inversion has been attributed to nucleophilic attack on an ion pair intermediate.¹⁷⁻²⁰ As illustrative examples, results of the acetolysis of the vinyl triflates **1a-c** in the presence of sodium acetate are given in Scheme 2.^{19,20} The fraction of inversion ranges from 40 to 80%, and is smaller the more stable the intermediate cation; β -alkyl substitution

**Scheme 3**

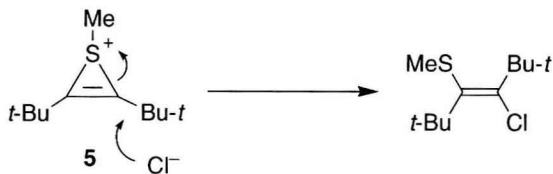


Scheme 4

stabilizes vinyl cations, as discussed below. In less nucleophilic solvents such as trifluoroethanol and trifluoroacetic acid the fractions of inversion are also much smaller (<10%).^{18,20} More stabilized vinyl cations, with e.g., an α -aryl substituent, lead to products of stereoconvergence. These trends are consistent with a change of mechanism from ion pair to free ion with increasing stabilization of the cations.

The intramolecular processes outlined in Scheme 3 occur formally with inversion of configuration at the electrophilic carbon. Example (1) is participation of a nucleophilic neighboring group, where the nucleophile is constrained to attack in-plane, while example (2) is the microscopic reverse of the first one, and the preferred path must again be in-plane attack. These reactions are postulated to occur via the $S_NV\sigma$ pathway to give the inverted product.²¹⁻²³ Their consecutive occurrence results in an anchimerically assisted reaction, and the net stereochemical outcome is retention of configuration due to double inversion. The overall mechanism of this type of reaction can be classified as S_NV1 , since the corresponding process in the solvolysis of saturated aliphatic derivatives is classified as an S_N1 reaction with neighboring group participation.

Participation of β -sulfur,²⁴ β -iodine,²⁵ and β -aryl groups²⁶ has been reported for the solvolysis of the vinylic substrates 2–4 (Scheme 4). Each of the reaction steps occurs with inversion, and the overall process results in retention of configuration. The cyclic 3-membered thiirenium ion 5 also gave exclusively inverted



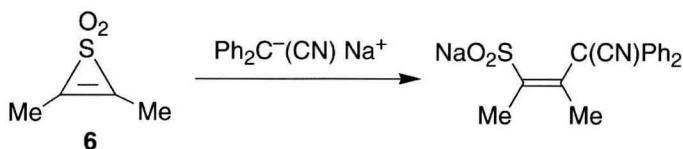
Scheme 5

nucleophilic substitution product (Scheme 5).²⁷⁻²⁹ However, retention of configuration was observed for the reaction of the neutral cyclic substrate, thiirene 1,1-dioxide **6** (Scheme 6).³⁰

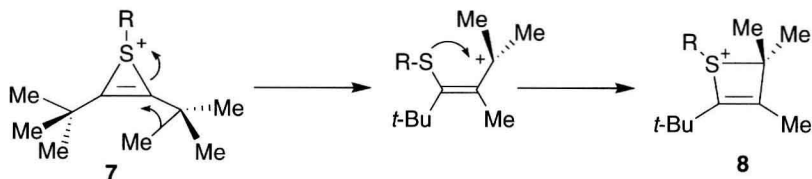
The intramolecular transfer of the nucleophilic group in Scheme 7 is also claimed to be an $S_NV\sigma$ reaction.^{22,23} The anionotropic rearrangement of the di-*tert*-butylthiirenium ion **7** into the thietium ion **8** involves the stereospecific backside attack of the internal methide at the unsaturated carbon.

Examples of acyclic vinylic systems that undergo nucleophilic substitution with complete inversion of configuration are very rare. The reaction of 1,2-dibromo-1,2-difluoroethene (**9**) with *p*-toluenethiolate affords products of apparently inverted structure without loss of stereochemical purity (Scheme 8).³¹ However, the authors are not sure whether this is due to the stereospecificity of the reaction or to the thermodynamic stabilities of the products.

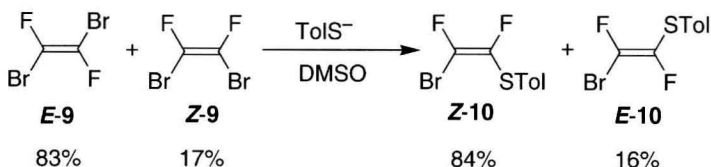
An unambiguous example is the nucleophilic substitution of 1-alkenyl(aryl)iodonium salts with halide ions (Scheme 9).³² 1-Decenyl(phenyl)iodonium tetra-



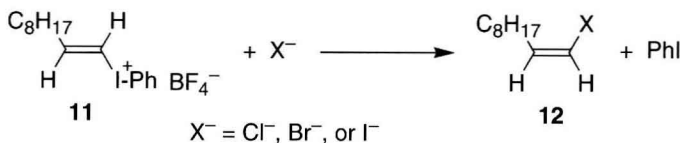
Scheme 6



Scheme 7



Scheme 8



Scheme 9

fluoroborate (**11**) gave the completely inverted haloalkene **12** when it reacted with chloride, bromide, or iodide ions. Details of this reaction are discussed in a section below (see Scheme 14).

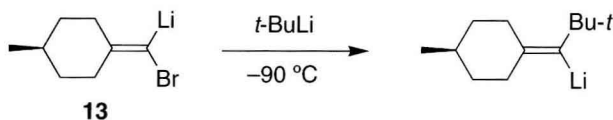
The nucleophilic substitution of the alkylidene carbenoid 1-bromo-1-lithioethene **13** with *tert*-butyllithium stereospecifically gives the inverted product (Scheme 10).^{33–35} This could be an $S_NV\sigma$ reaction.

An S_N2 -type substitution at the sp^2 -hybridized nitrogen atom of a C=N bond has recently been reported for the acid-catalyzed intramolecular reaction of oxime **14** (Scheme 11).³⁶ The results have been rationalized by theoretical calculations.

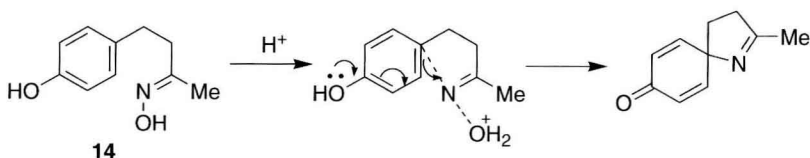
THEORETICAL CONSIDERATIONS

It has long been believed that in-plane nucleophilic substitution at vinylic carbon ($S_NV\sigma$) is an unfavorable process, partly due to steric reasons.^{7,8} The nucleophilic attack occurs at the vacant orbital of the electrophilic substrate, and the LUMO of alkenes was generally thought to have π symmetry and not σ symmetry (σ^* orbitals are in general higher in energy than π^* orbitals). This would make perpendicular attack at the vinylic carbon (π^*) by a nucleophile more favorable than in-plane attack (σ^*). Early theoretical calculations for the system $H_2C=CH_2 + H^-$, using the extended Hückel method, in fact showed a very high energy barrier (326 kJ mol^{-1}) for the in-plane $S_NV\sigma$ reaction and a low barrier (75 kJ mol^{-1}) for the perpendicular π attack.⁹ Later theoretical studies undertaken in the 1970s and 1980s focused on the perpendicular and not on the in-plane reactions. Inspired by experimental indications that the in-plane S_NV process is feasible, more sophisticated MO calculations on such reactions were undertaken in the 1990s. The results thereof are at variance with the conclusions of the early calculations.

First, it was shown that the LUMO of vinylic substrates is not necessarily of π symmetry. For some classes of vinylic compounds the LUMO is a σ^* orbital (Table 1).¹³ While simple vinylic compounds such as vinyl chloride and triflate (entries 4 and 5) have an anticipated π^* orbital as LUMO, charged substrates (entries



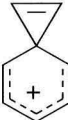


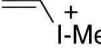

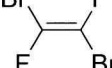
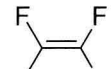
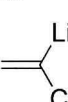


Scheme 10



Scheme 11

Table 1 Energies of the lowest vacant orbitals (in hartree) with π and σ symmetry for the vinylic portion of some model substrates

No.		LUMO (symmetry)	LUMO + 1 (symmetry)
1		-0.1046 (σ)	-0.0954 (π)
2		0.0819 (π)	0.1878 (σ)
3		-0.1395 (σ)	-0.0713 (π)
4		0.1454 (π)	0.1824 (σ)
5		0.1328 (π)	0.1811 (σ)
6		-0.065 (σ) ^a	-0.029 (π) ^a
7		-0.106 (σ) ^a	-0.035 (π) ^a
8		0.1226 (σ) ^b	0.1421 (π) ^b
9		0.1355 (σ) ^b	0.1391 (π) ^b
10		0.0476 (σ)	0.1195 (π)

Calculated at 6-311G**//3-21G* (Ref. 13) unless noted otherwise.

^aCalculated at 6-31G* (MP2).¹⁴

^bCalculated at 3-21G**//3-21G*.¹³

1, 3, 6, and 7) have a σ^* orbital as LUMO. Thus, frontier orbital considerations rationalize the observed inversion in the S_NV reactions of the charged substrates in Schemes 5, 7 and 9. In accordance with the experimental observation of substitution with retention in Scheme 6, the cyclic sulfone (entry 2) has a LUMO with π symmetry. Polyhaloethenes have lowest σ^* and π^* orbitals which are very close in energy to