Polar Acetalization and Transacetalization in the Gas Phase: The Eberlin Reaction†

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† Dedicated to Helmut Schwarz and Nico Nibbering in admiration of their work.

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1. Introduction

Ion/molecule reactions performed in the low pressure, very dilute environment of the mass spectrometer provide access to key properties and intrinsic reactivities of a great variety of solvent- and counterion-free gaseous ions and as such constitute a powerful tool for chemical studies.[1−10] Mass spectrometry is applicable to species as simple as protons and bare metal ions,[11−13] to much more complex polyatomic organic,[4,6,14] organometallic,[15,16] and bio-organic ions,[17,18] and to exotic and elusive anions and cations so far inaccessible in the condensed phase. These diverse ionic species have been formed, isolated, measured, and then allowed to react in the gas-phase environment by a variety of MS techniques able to determine the masses, the structures (viz, the connectivities) of the ionic reaction products, and a number of their physicochemical properties. The importance of ionic species in chemical processes is hard to overstate because they constitute the key reactants, intermediates, and products of major chemical reactions and processes in a wide range of milieux, including flames[19−21] and plasmas,[22,23] industrial semiconductor production,[24,25] interstellar space,[26,27] chemical and pharmaceutical manufacturing,[28] and many vital biosystems. The diverse information on ion properties, reactivity, thermochemistry[29−31] and dynamics[32−35] that gas-phase ion/molecule reaction studies provide has therefore been indispensable for fundamental chemical research and for understanding chemical processes involving ionic species.

Ion/molecule reactions have also contributed significantly to the elucidation of organic reaction mechanisms, helping to bridge the gap between gas-phase ion chemistry and condensed-phase organic chemistry. Many classical organic reactions have been studied in the gas phase using MS methods. They include nucleophilic substitution reactions,[6,36−41] the Friedel−Crafts acylation,[42] the Diels−Alder cycloaddition,[43−46] the Wittig reaction,[47,48] the Reformatsky reaction,[49] Michael addition,[50,51] the Kolbe reaction,[52] the Cannizzaro reaction,[53] Claisen−Schmidt reactions,[54] the Meerwein−Ponndorf−Verley reduction/Oppenauer oxidation,[55,56] the pinacol,[57] Claisen,[58,59] Hofmann,[60,61] Cope,[62,63] Lossen,[64,65] and Wolff rearrangements,[66] and the Fischer indole[57] and cumulene syntheses.[67] Recently, with the advent of electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI), mass spectrometry has become much more widely used as an instrumental tool in inorganic and organometallic chemistry, including its use to identify short-lived transient intermediates, for example, those operative in catalytic cycles.[68,69] Coupling of ESI and APCI ion sources to methods for the study of ion/molecule reactions in the

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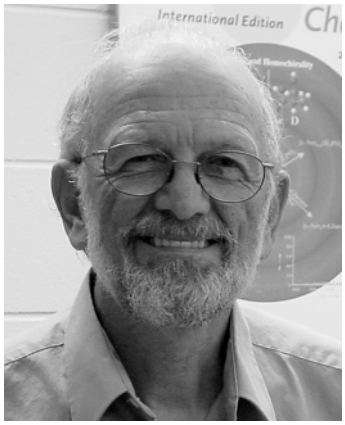
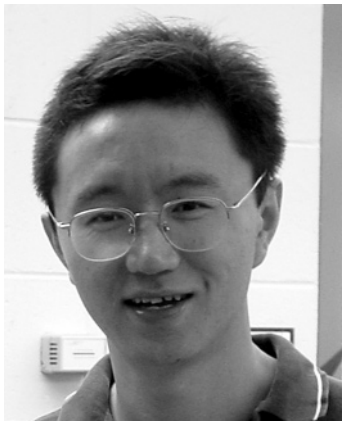


Dr. R. Graham Cooks was educated at the University of Natal, South Africa, and at Cambridge University in Great Britain. Since 1990, he has been Henry Bohn Hass Distinguished Professor of Chemistry at Purdue University. Dr. Cooks is interested in many aspects of mass spectrometry, including fundamental phenomena associated with collisions of ions and molecules in the gas phase and at surfaces, ionic fragmentation and reaction mechanisms, and analytical applications. He has for many years been engaged in research using tandem mass spectrometry and is currently employing ion/molecule reactions to recognize functional groups in polyfunctional compounds and collision-induced dissociation of cluster ions to measure such fundamental thermochemical properties as proton affinities. His interests also include separation and collection of compounds using ion soft landing, high-throughput analysis, and biological tissue imaging, all using forms of mass spectrometry. Several new types of mass spectrometers have been constructed in Dr. Cooks' laboratory, most recently miniature instruments for in situ analysis. He has made contributions to the development of desorption ionization and tandem mass spectrometry including the recent ambient mass spectrometry method of desorption electrospray ionization. His work on the kinetic method of measuring thermochemical quantities is one outcome of his interest in ion structure and fragmentation mechanism. Dr. Cooks has authored over 700 publications and served as Ph.D. thesis advisor to 95 Ph.D. students.



Hao Chen was born in Anhui, China, in 1975. He obtained his B.S. degree in Chemistry from Wuhan University in 1996 and his Ph.D. degree under the supervision of Professor R. Graham Cooks from Purdue University in 2005, where his research focused on thermochemical measurements and gas-phase ion chemistry, as well as their analytical applications using mass spectrometry. He is currently a postdoctoral research associate with Professor Cooks and is working on atmospheric pressure ion/molecule reactions and reactive desportion electrospray ionization (DESI).

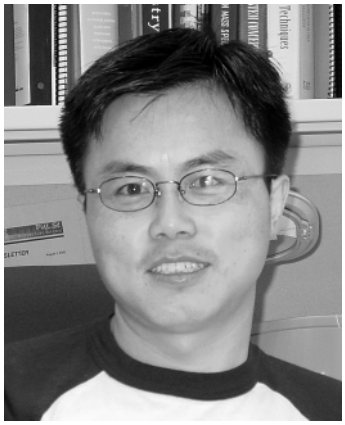
Marcos N. Eberlin was born in Campinas, Brazil, in 1959 and received his Ph.D. from the State University of Campinas (UNICAMP) in 1988. In 1989, he joined the group of Prof. R. G. Cooks for his postdoctoral studies at Purdue University in the USA. In 1991, he returned to UNICAMP and established the Thomson Mass Spectrometry Laboratory, which is today a Brazilian reference center for mass spectrometry. His research interests include the analytical, synthetic, and fundamental applications of gas-phase ion/molecule reactions and the development and applications of new mass spectrometric techniques in all branches of science.

Xubin Zheng was born in Hunan, China, in 1968. He obtained his B.S. degree in Chemistry from Peking University in 1990 and his Ph.D. degree under the direction of Professor R. Graham Cooks from Purdue University in 2002, where he carried out his graduate work in the areas of gas-phase ion–molecule reactions and thermochemical determinations using mass spectrometry. He is currently a Research Scientist II in the Department of Drug Metabolism at Gilead Sciences, a biopharmaceutical company headquartered in Foster City, California.

gas-phase yields detailed information about single reaction steps of catalytic cycles[70] and allows the study of transient intermediates that have previously not been accessible by condensed-phase techniques on both a qualitative and a quantitative level.[71]

The mechanisms of organometallic reactions involving nonvolatile reagents, such as the Grubbs metathesis reaction,[72,73] the Gilman reaction,[74] the Heck reaction,[70] the Baylis−Hillman reaction,[75] the Petasis olefination reaction,[76] the Ziegler−Natta olefin oligomerization,[77] the Stille reaction,[78] Pd-catalyzed C−C bond formation,[79] and nucleophilic substitution reactions,[80,81] as well as the structure of the Grignard reagent[82,83] and the cocatalytic role of ionic liquids in organometallic reactions,[84] have been successfully explored by various MS techniques. These studies have confirmed reaction mechanisms and also have deepened our understanding of the role that solvation and ion pairing play in determining the outcomes of ionic reactions, even to the point of suggesting novel and superior catalysts in solution.[85,86]

With the aim of understanding bulk solution chemistry from gas-phase studies, a considerable amount of effort using high-pressure mass spectrometry[87−90] and new ionization methods such as ESI has already addressed the reactivity of microsolvated ions.[91] The partially solvated ions studied include core hydroxide,[92] acylium,[93] halide,[94] alkali metal,[95]



Weiguo Andy Tao is an assistant professor in the Department of Biochemistry at Purdue University. He started his Ph.D. career in 1997 in the laboratory of Professor R. Graham Cooks on applications of mass spectrometry for gas-phase ion–molecule reactions and enantiomeric determination. After receiving his Ph.D. in December 2001, he joined the Institute for Systems Biology in Seattle, Washington, as a Damon Runyon Cancer Research Postdoctoral Fellow. His current research program focuses on the development of novel techniques for proteomic research and the application of proteomics to solve important biological issues.

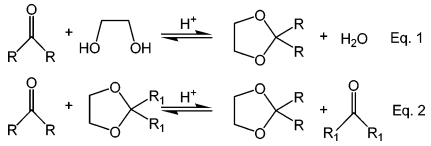
transition metal,[96] and nucleic acid ions[97] solvated with single or multiple molecules of water, alcohols, and other solvent species of organic and atmospheric interest. Such ions are much more relevant to solution chemistry than the radical cations of traditional electron ionization (EI) mass spectrometry. These newer studies provide information on ion solvation energy, as well as rate constants, isotope effects, and product distributions, as a function of the cluster size and composition, increasing our knowledge of solvation at the molecular level.

Ion/molecule reactions are also a powerful if underutilized means of determining the structures of gaseous ions and have been used in conjunction with or as an alternative to the standard process of collision-induced dissociation (CID, a process in which the selected precursor ions are subjected to collisions with an inert target gas to produce fragment ions). Both experiments are performed using tandem mass spectrometry.[3,15,98,99] Because ion/molecule reactions are normally fast and efficient in the gas phase and highly sensitive to the nature of functional groups including fine structural variations such as relative positions of functional groups, product distributions often provide key and diagnostic information for structural characterization of both reactant ions and neutral molecules.[100−103] For instance, an early and classical application of ion/molecule reactions showed that the simplest amino acid, glycine, adopts an uncharged form in the gas phase, not the zwitterionic form normally found in solution.[104,105] Again, a classical group of isomeric gaseous ions, $C_7H_7^+$ (benzyl, tropylium, and toluyl cations), which are very difficult to distinguish by CID, are easily differentiated through ion/molecule reactions involving electrophilic attack on toluene[106] and dimethyl ether.[107] More interestingly, numerous examples of stereospecific ion/molecule reactions reported in the gas phase[108−110] are useful for the distinction of stereoisomers, including cases in which NMR encounters severe problems. As an example, consider the gas-phase reaction of Ti^+ with $C_6H_6D_6$ generated by hydrogenation of C_6D_6 with a cobalt catalyst. The ion/molecule reaction exclusively yields $Ti(C_6H_6)^+$ and $Ti(C_6D_6)^+$, revealing a greater than 99.5% all-*syn*-hydrogenation of C_6D_6 by the cobalt catalysis.[111] Many interesting structural elucidation applications of ion/molecule reactions performed under chemical ionization (CI) conditions[112,113] have been well documented in previous reviews.[103,114,115] Trimethylborate, for example, an unusual CI reagent gas, reacts stereospecifically with diols and mono- and disaccharides.[116] Another interesting example is the use of selective CI with dimethyl ether to probe the location and number of substituents on macrocyclic lariat ethers.[102]

Ion/molecule reactions also play an important role in the synthesis of elusive ionic species that are not easily accessible in solution or from direct ionization or dissociation of neutral molecules.[117−121] Exotic examples include nonclassical distonic ions (a radical cation or anion in which the charge site and the spin site are not both formally located in the same atom or group of atoms).[118,121] A historic but still remarkable example is the ready preparation of the methionium ion, CH_5^+, by the gas-phase ion/molecule reaction of $CH_4^{+\bullet}$ with CH_4.[122] This pentacoordinated carbocation was long regarded with some suspicion by organic chemists and only many years after the ion/molecule discovery was it indicated to exist in superacid media by Olah.[123] Ion/molecule reactions also have biological significance because they can be used to probe the gas-phase structures of biomolecules such as proteins[17,124−127] and nucleosides[128] and to unravel the detailed structures of molecular aggregates such as the homochiral serine octamer.[129−131] For instance, hydrogen/deuterium exchange experiments between protein ions and deuterated reagents can provide insights into the conformation of gas-phase proteins based on a generalization that the native folded state exchanges a smaller number of hydrogens than unfolded conformers because labile hydrogens are tied up by hydrogen bonding in the former.[126] Also, specific peptide bond cleavage using ion/molecule reactions[132−134] has been reported to be useful for protein sequencing.

Acetalization of aldehydes and ketones with diols is a classical and general reaction of great synthetic utility in solution (Scheme 1, eq 1).[135,136] This facile reaction is widely

Scheme 1



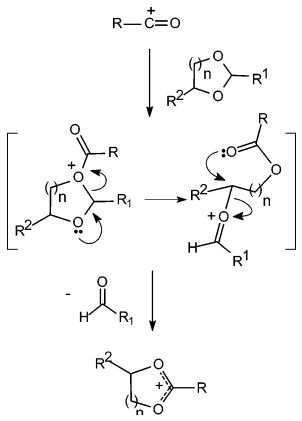
employed to protect carbonyl compounds against addition by nucleophiles or reduction at the carbonyl group in basic media. Deprotection can be easily performed by mild acid hydrolysis. Transacetalization with a cyclic acetal is also a classical strategy used in solution, either to protect carbonyl compounds or to regenerate the acetal-protected carbonyl compounds (Scheme 1, eq 2).[137,138] This reaction is particularly useful when the direct reaction of a ketone with an alcohol gives poor yields.

This review concerns the remarkable gas-phase ion/molecule reaction counterpart of the "neutral" acetalization and transacetalization reactions just mentioned. In its model version, it occurs via polar transacetalization and has been performed by tandem mass spectrometric techniques using isolated (by mass selection) gaseous ions under controlled reaction conditions of ion translational energy and neutral reagent pressure. The model reaction employs amphoteric acylium ions (bearing both a Lewis acidic and a basic site) and neutral cyclic acetals and yields resonance-stabilized cyclic ionic acetals via the elimination of neutral aldehydes

or ketones. Now known as the Eberlin reaction, this bimolecular gas-phase process has been the subject of extensive studies on mechanism, generality, and fundamental, analytical, and synthetic applications since its discovery a decade ago by Eberlin and Cooks.[139] The Eberlin reaction is often found to be facile; in many cases, the cyclic ionic acetals are formed nearly exclusively (reactant ion conversion to products occurs in yields up to 100%, measured as is usual by product to reactant ion intensities). Besides the vacuum (dilute gas-phase) environment inside mass spectrometers, the reaction has also been found to occur both at reduced pressure and under atmospheric pressure, as well as in solution.[140] It is this range of reaction conditions that makes Eberlin reactions potentially so valuable in connecting reactions in these different media.

In the Eberlin transacetalization (Scheme 2), initial gas-

Scheme 2

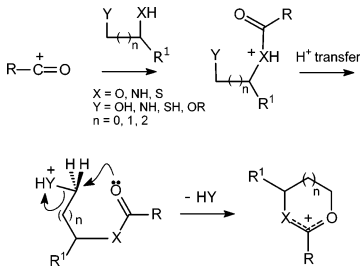


phase O-acylation is followed by fast and thermodynamically favored ring opening and then recyclization with the release of the previously acetal-protected neutral carbonyl compound and the formation of a cyclic ionic acetal, that is, formation of the resonance stabilized cyclic 1,3-dioxolanylium (n = 1) or 1,3-dioxonium ion (n = 2).

Polar transacetalization (Scheme 2) therefore resembles condensed-phase transacetalization, in which the reactant acylium ion and the cyclic ionic acetal product mimic the free reactant carbonyl compound and the cyclic acetal product of the "neutral" condensed-phase reaction, respectively. In addition, just as hydrolysis of cyclic acetals regenerates neutral carbonyl compounds in solution, so CID of the gaseous cyclic ionic acetals re-forms the acylium ions. Mechanistically, the Eberlin reaction (Scheme 2) involves nucleophilic addition of the neutral acetal to the acylium ion in one step and elimination of a neutral carbonyl compound during a second ring closure step. By contrast, in the acetalization of a carbonyl compound with a diol (Scheme 1, eq 1), there is one step of nucleophilic addition of the diol to the acid-activated carbonyl substrate and one step of water elimination before ring closure takes place. In the neutral variant of transacetalization reactions (Scheme 1, eq 2), the acetal reactant first undergoes acid-catalyzed hydrolysis to form the diol, which subsequently acetalizes the carbonyl reactant. The prototype Eberlin reactant ions are amphoteric acylium ions ($R-C^+=O$). Many other amphoteric ions bearing both a Lewis acidic and a basic site have also been employed including thioacylium ($R-C^+=S$),[139,141] carboxonium ($H_2C=O^+-R$),[142] carbosulfonium ($H_2C=S^+-R$),[142] distonic or distonoid radical acylium ($^{\bullet}R-C^+=O$, R = alkyl, allyl, or phenyl),[143,144] singly charged diacylium ($O=C=N^+=C=O$),[145,146] sulfinyl ($R-S^+=O$),[141,147] arylsulfenium (ArS^+),[148] borinium $(RO)_2B^+$,[149] silylium $((RO)_3Si^+)$,[150] phosphonium ($R_2P^+=O$),[149,151] arylnitrenium ($ArNH^+$),[152] nitronium (NO_2^+),[153] and hetarynium ions (2-pyridyl, 2-pyrrolyl cations, and their analogues).[154] As a result of the multiplicity of suitable reactant ions and neutrals, various heterocycle ionic systems are successfully generated via polar transacetalizations.

A major variant of the model Eberlin transacetalization reaction (Scheme 2) is the Eberlin acetalization reaction (Scheme 3).[155,156] This latter reaction of gaseous acylium ions

Scheme 3



with 1,2-diols and higher homologues and their sulfur, nitrogen, monoether, or monothioether analogues occurs by a mechanism that parallels that of polar transacetalization (Scheme 2) except for the difference in the type of neutral reagent and neutral product. It also contrasts with carbonyl compound acetalization in solution: initial acylation is followed by intramolecular proton transfer and intramolecular HY displacement with the anchimeric assistance of the neighboring acyl group (Scheme 3). Multiple stage MS^2 and MS^3 experiments (MS^2 and MS^3 refer to two-stage and three-stage tandem mass spectrometry experiments, respectively),[155,156] together with ^{18}O-labeling and ab initio calculations, have demonstrated that gas-phase polar acetalization forms the same class of cyclic ionic acetals (Scheme 3) as that formed via polar transacetalization (Scheme 2). Both Eberlin acetalization and transacetalization have been shown to be quite general for acylium ions and their analogues and to display similar characteristics and applications.

Attention has been drawn to many interesting aspects of the Eberlin reaction, which can be summarized as follows: (i) The reaction preference, selectivity, and exothermicity are often very high; often the highly stable Eberlin product is by far the major or even the exclusive ion/molecule reaction product, and it is formed in high yield. (ii) The reaction offers a way to investigate the nature of deprotecting or protecting group chemistry in the gas phase while suggesting new reagents for application in solution. (iii) The reaction functions as a structurally diagnostic and class-selective gas-phase reaction providing fine structural details (substituent positions and ring/chain sizes) of both the reactant ions and the neutral cyclic acetals, diols, and analogues. (iv) It can be used to distinguish isomers, and as such, it has been applied to distinguish diagnostic acylium ions and as part of a strategy for the "MS-only" assignment of positional isomers.[157] (v) It provides concise new routes to the synthesis of a variety of heterocycles in the gas phase.[152] (vi) The reaction can be performed efficiently under ambient conditions using ESI and APCI, which greatly expands its applicability to heavier and more polar molecules than those normally employed in high-vacuum experiments.[158] (vii) It serves as a staging ground for attempts to

explore details of the intrinsic nature of a particular organic reaction across different phases.

The review covers major aspects of this remarkable gas-phase reaction including the experimental methods employed, the prototype Eberlin reaction and its variants with discussions on reaction mechanism, regioselectivity, substituent effects, and relationships with analogous condensed-phase reactions and other ion/molecule reactions. This review also discusses the broad scope of the Eberlin reaction describing many analytical, synthetic, and fundamental applications of this versatile ion/molecule reaction.

2. Experimental and Theoretical Methods

Several mass spectrometers and methods for their operation have been developed to study ion/molecule reactions in detail under controlled conditions. They include flow instruments such as flowing afterglow mass spectrometers[159−161] and selected-ion flow tubes (SIFT),[162−164] ion trapping instruments including Fourier transform ion cyclotron resonance (FT-ICR)[165−168] and quadrupole ion trap (QIT) mass spectrometers,[169,170] and tandem mass spectrometers such as multiple-sector tandem mass spectrometers,[171] guided ion beam tandem mass spectrometers,[172−175] triple quadrupoles (QqQ, Q signifies the 1st or 3rd quadrupole and q refers to the collision/reaction quadrupole cell),[101,176] and pentaquadrupoles.[177−179] In addition, more specialized instruments have been developed for special purposes such as crossed beam or merged beam instruments for the study of thermal collisions[180,181] and pulsed electron high-pressure mass spectrometers[87,182−184] for evaluation of ion/molecule equilibria used to provide thermochemical information. Tandem mass spectrometers are particularly well suited to the study of ion/molecule reactions. For instance, triple quadrupoles are extraordinarily convenient and efficient for MS^2 experiments in a *tandem-in-space* mode, can be operated over a range of ion kinetic energies (from zero to a few hundred electronvolts) to permit access to reactive and dissociative collisions, and give unit mass resolution for the pre- and post-collision ions, as well as high ion transmission in the "rf-only" quadrupole reaction cell ("rf-only" means no DC voltage applied on the quadrupole). These instruments also display high tolerance to poor vacuum and ease of operation and software control. In addition to inheriting the advantages of triple quadrupoles, the more complex but considerably more powerful pentaquadrupoles can be used to carry out triple-stage mass spectrometry (MS^3) experiments and therefore overcome an important limitation of triple quadrupoles for ion/molecule reaction studies; that is, they provide the ability to obtain structural information on the products of the reactions of mass-selected ions. Pentaquadrupole mass spectrometers are particularly well suited to such studies because they allow the full range (all 21 types)[185] of MS^0 to MS^3 experiments to be easily accessed, with easy on-line mass-selection and control of the reactant and product ions.[186] A detailed description of the instrumental aspects and the applications of pentaquadrupoles in performing ion/molecule reactions has been published.[187]

Two home-built pentaquadrupoles[186,187] have played an important role in the study of the Eberlin reaction, and one is shown schematically in Figure 1. Pentaquadrupoles consist of three mass-analyzing quadrupoles (Q1, Q3, and Q5) and two reaction quadrupoles (q2 and q4). When a pentaquadrupole (QqQqQ) is used for double-stage mass spectrometry (MS^2) experiments, the reagent ions are normally generated by electron ionization or chemical ionization, mass-selected in Q1, and allowed to undergo ion/molecule reactions with neutral reagent introduced into q2 employing very low "near zero" electronvolt (typically nominal 0−1 eV) multiple collisions with the neutral reactant. These mild conditions have been shown to cool (approximately thermalize) both reactant and product ions and are particularly appropriate for the study of exothermic ion/molecule reactions, the rates of which typically decrease with increasing translational energy.[188] The resulting product ion mass spectra are recorded by scanning Q5 with both Q3 and q4 set in the rf-only mode. For pentaquadrupole MS^3 experiments, each desired product ion arising from q2 is mass-selected using Q3 and then allowed to collide with argon in q4 using energies typically within the 1−15 eV range. This allows product ion characterization by collision-induced dissociation.

Besides pentaquadrupoles, Eberlin reactions have also been successfully investigated using triple quadrupoles[152] and in a hybrid quadrupole orthogonal time-of-flight (Q-TOF) mass spectrometer,[158] demonstrating that such reactions can be performed in many commercial instruments. However, because the reaction time for the Eberlin reactions performed in the *tandem-in-space* instruments such as triple quadrupoles and pentaquadrupoles could not be precisely controlled, future reaction kinetic studies using *tandem-in-time* instruments such as FT-ICR and ion traps should be most rewarding.

Support of the experimental results was sought by ab initio potential energy computations. This information was used to justify the suggested reaction pathways, rationalize the feasibility of the proposed ion/molecule reactions, and determine the thermodynamically favorable products. For example, density functional theory (DFT) calculations were performed using the Gaussian program package.[189] Optimized geometries and energies were calculated using various modes such as B3LYP/6-31G(d), RHF/6-31G(d,p), and G2(MP2).

3. Prototype Eberlin Reaction

3.1. Reaction Mechanism

The prototype Eberlin transacetalization was first recognized from the observation that many gaseous acylium ions bearing different substituents (Scheme 2, R = alkyl, phenyl, hydroxyl, methoxy, alkylamine, chlorine, and vinyl) react with 1,3-dioxolanes to give resonance-stabilized cyclic ionic acetals (Scheme 2).[139] Polar transacetalization protects therefore the acylium ion $R-C^+{=}O$ in the form of the stable cyclic ionic acetal (gas-phase species of relatively low energy and very low reactivity) with the release of the neutral aldehyde or ketone previously formally protected in the form of the neutral cyclic acetal.

Figure 2 displays typical product ion mass spectra for Eberlin reactions of the gaseous $CH_3O-C^+{=}O$ acylium ion (*m*/*z* 59, an ion with moderate Eberlin reactivity, generated by EI of methyl acetate) with either 1,3-dioxolane or 2-methyl-1,3-dioxolane. Such a product spectrum is a record of all ionic products upon reaction of the mass-selected ion with the chosen neutral reagent. The same Eberlin product, a cyclic ionic acetal of *m*/*z* 103 (2-methoxy-1,3-dioxolanylium ion), is formed upon the release of either formaldehyde or acetaldehyde and constitutes the dominant product ion in both spectra. Minor products arise from competitive hydride abstraction and proton-transfer reactions (e.g., the ions of *m*/*z* 73 and 75 generated from 1,3-dioxolane by hydride abstraction and protonation, respectively, seen in Figure 2a).

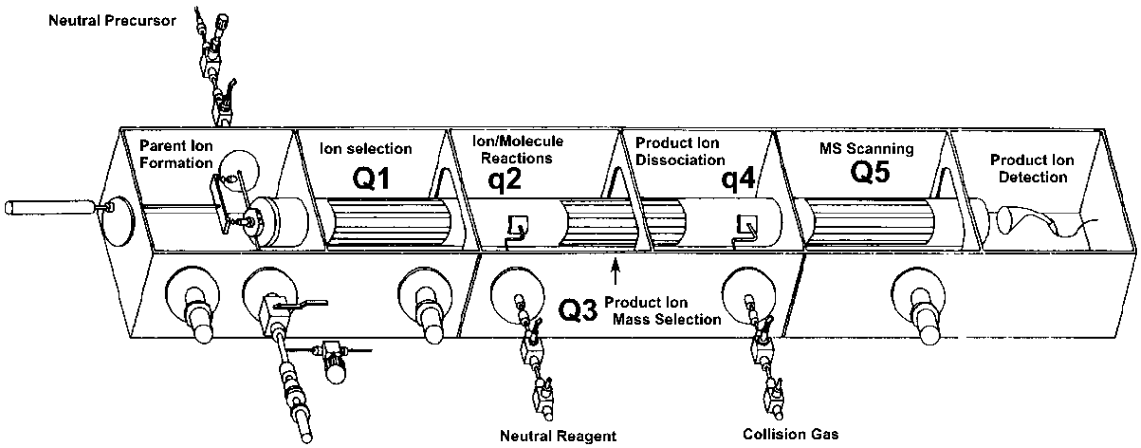


Figure 1. Schematic of a pentaquadrupole mass spectrometer, an instrument commonly used to perform gas-phase Eberlin reactions. Note the in-line arrangement of the three mass analyzers (Q1, Q3, and Q5) and the two rf-only quadrupole reaction chambers (q2 and q4). In a typical ion/molecule reaction experiment, ions are generated in the ion source, purified (mass-selected) using Q1, and set to undergo Eberlin reactions under controlled conditions (collision energy, pressure, and sometimes reaction time) with a neutral cyclic acetal introduced into q2. Each product ion is subsequently mass-selected by using Q3 and structurally analyzed often by collision-induced dissociation in q4, where the final product ions formed in these processes are detected by scanning Q5. Reprinted with permission from ref 147. Copyright 1996 Royal Society Chemistry.

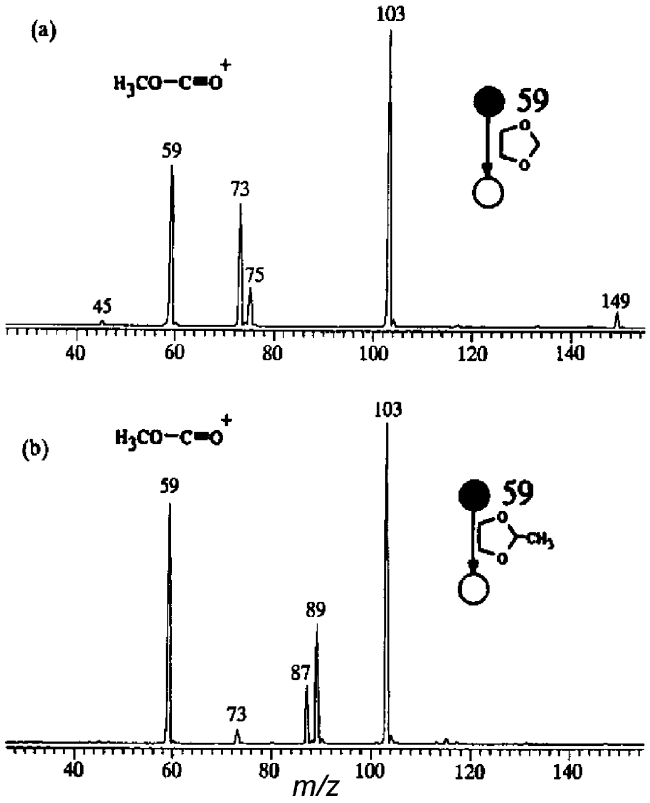


Figure 2. Double-stage MS^2 mass spectra showing products of the ion/molecule reactions of the acylium ion, $CH_3O-C^+=O$, of *m*/*z* 59 with (a) 1,3-dioxolane and (b) 2-methyl-1,3-dioxolane. Note the extensive formation in both cases of the Eberlin product ion of *m*/*z* 103, together with products of proton transfer and hydride abstraction side reactions at (a) *m*/*z* 73 and 75 and (b) *m*/*z* 87 and 89. Reprinted with permission from ref 139. Copyright 1993 John Wiley & Sons Limited.

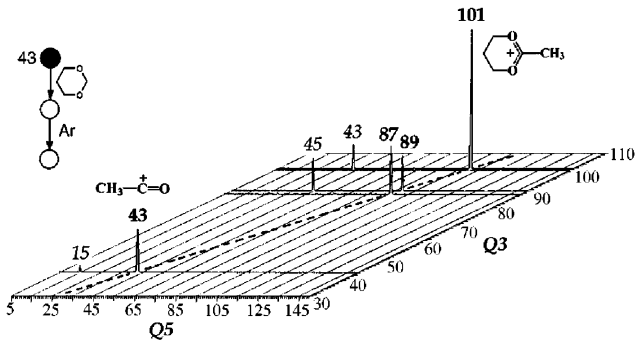


Figure 3. Triple-stage MS^3 product domain mass spectrum showing products of the ion/molecule reaction of the acetyl cation, $CH_3-C^+=O$, of *m*/*z* 43 with 1,3-dioxane. All the reaction products (bold numerals) are displayed along the diagonal dashed line, while the 15 eV CID fragments (italic numerals) of each product ion are displayed along the horizontal Q5 axis. Reprinted with permission from ref 141. Copyright 1997 Royal Society Chemistry.

Structures of Eberlin products have been clearly determined by their characteristic dissociation behavior and by isotopic labeling. Just as hydrolysis of cyclic acetals or acetals regenerates neutral carbonyl compounds in solution, so CID of gaseous cyclic ionic acetals tends to re-form the acylium ions in high yields. Figure 3 illustrates this tendency by showing the MS^3 data domain acquired using a pentaquadrupole (QqQqQ, Figure 1). This comprehensive experiment is done by mass-selecting the acetyl cation $CH_3-C^+=O$ of *m*/*z* 43 using Q1, scanning sequentially both Q3 and Q5, and performing Eberlin reactions with 1,3-dioxane in q2 and dissociative collisions with argon in q4. This interesting type of MS^3 experiment allows a detailed three-dimensional view of a whole set of processes by displaying in a single spectrum all the products of the mass-selected reactant ion, where each such product is associated with its characteristic CID fragment ions. Across the diagonal (the Q3 axis), the surviving reactant acylium ion of *m*/*z* 43 and all its reaction products of *m*/*z* 87, 89, and 101 (bold numerals) are displayed, whereas the CID fragment ions (italic numerals) of each individually selected product ion are detected and displayed across the Q5 horizontal axis. The reactant ion dissociates to yield CH_3^+ by CO loss. The protonated 1,3-dioxane product of *m*/*z* 89 fragments to the ion of *m*/*z* 45 by loss of a neutral molecule of 44 Da; the Eberlin polar transacetalization product of *m*/*z* 101 loses a neutral molecule of 58 Da to regenerate the reactant acetyl cation of *m*/*z* 43, while the hydride abstraction product of *m*/*z* 87 does not

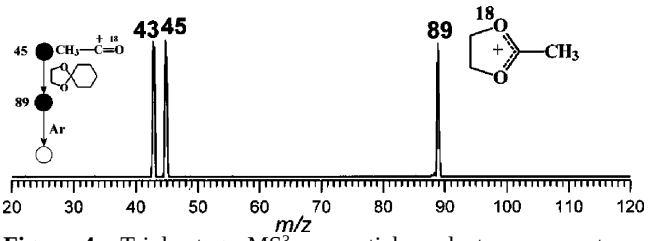
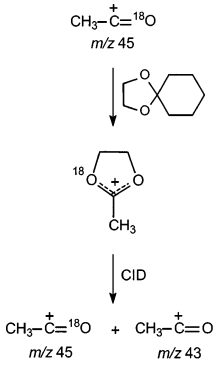


Figure 4. Triple-stage MS^3 sequential product mass spectrum showing dissociation fragments of the products of the Eberlin reaction of $CH_3C^+{=}{}^{18}O$ with 2,2-pentamethylene-1,3-dioxolane. Note that the selected isotopologue ion of *m*/*z* 89 is generated only from the ion of *m*/*z* 45 and dissociates to the same extent to both the labeled ($CH_3C^+{=}{}^{18}O$ of *m*/*z* 45) and unlabeled ($CH_3C^+{=}O$ of *m*/*z* 43) product ions, which corroborates a cyclic structure for the ion/molecule reaction product. Reprinted with permission from ref 190. Copyright 1997 American Chemical Society.

dissociate to a measurable extent under the collision conditions employed in q4.

Authentic ions generated by dissociative electron ionization of appropriate precursors such as 1,4-dioxospiro[4,5]-decane[139] display the same CID behavior as the Eberlin reaction products. These data go a long way to establish the structure of the Eberlin products. Labeling experiments using ^{18}O have also been shown to fully corroborate the cyclic ionic acetal structures.[190] For instance, the cyclic ionic acetal generated by the Eberlin reaction of $CH_3C^+{=}{}^{18}O$ with 2,2-pentamethylene-1,3-dioxolane upon CID forms both the labeled $CH_3C^+{=}{}^{18}O$ (*m*/*z* 45) and unlabeled $CH_3C^+{=}O$ (*m*/*z* 43) acylium ion to nearly the same extent (Figure 4), and such a complete O-scrambling process requires the formation of a cyclic and symmetrical structure like that proposed in Scheme 4.

Scheme 4



In addition to characterization of the product, strong evidence for the mechanism of the Eberlin polar transacetalization has also been acquired. Analogous to the protection of neutral aldehydes or ketones in the condensed phase, polar transacetalization of acetals with gaseous acylium ions starts with O-acylation and is followed by a ring opening and then a cyclization process in which neutral carbonyl compounds are eliminated and the cyclic ionic acetals are formed (Scheme 2). Theoretical calculations have demonstrated that polar transacetalization is by far the most exothermic reaction channel and that the initial formation of the O-acylation adduct is its main driving force. Typical data are shown in Figure 5 for the reaction of CH_3CO^+ with 1,3-dioxolane.[190] The high exothermicity of O-acylation (−25.1 kcal/mol) and of the subsequent steps leading to the formation of the Eberlin product makes polar transacetalization the most thermodynamically favorable reaction

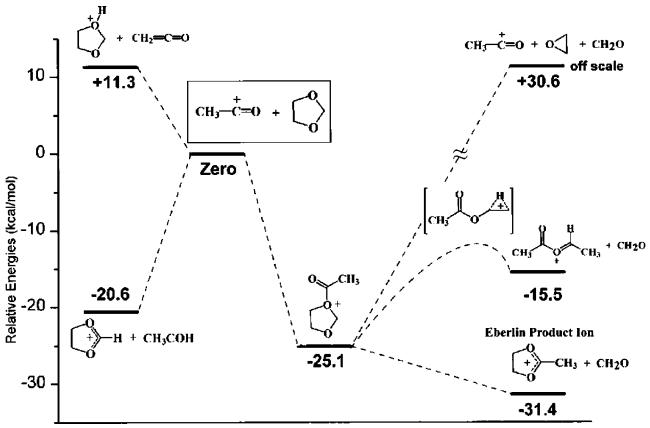
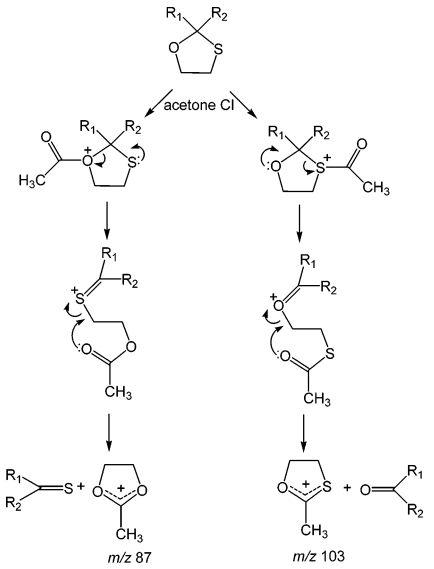


Figure 5. Ab initio potential energy surface diagrams for the reaction of the acetyl cation, $CH_3{-}C^+{=}O$, with 1,3-dioxolane. Note that the Eberlin product ion is by far the most thermodynamically favored and the reaction driving force is provided by initial O-acylation. The activation barriers for the Eberlin reaction are not shown. Reprinted with permission from ref 190. Copyright 1997 American Chemical Society.

compared with other possible competitive reactions. Hydride abstraction is exothermic (−20.6 kcal/mol) but less so than transacetalization (−31.4 kcal/mol), whereas proton transfer is endothermic (+11.3 kcal/mol) and therefore thermodynamically unfavorable.

Interestingly, the key steps in the Eberlin reaction, the ring opening and the ring reclosure with the elimination of a neutral carbonyl compound, have been also observed by Vainiotalo et al.[191] in the decomposition of various acylated dioxolanes and oxathiolanes generated by chemical ionization using acetone as the reagent gas. The acylated dioxolanes were found to yield the cyclic Eberlin reaction products, dioxolanylium ions, upon CID, while acylated oxathiolanes (Scheme 5) decompose to both oxathiolanylium (*m*/*z* 103)

Scheme 5



and dioxolanylium ions (*m*/*z* 87), depending on the initial acylation position on oxathiolanes (Figure 6). This result provides additional evidence for the proposed Eberlin reaction mechanism as shown in Scheme 2.

3.2. Reaction Efficiency and Regioselectivity

Substitutents on the neutral cyclic acetal reagents are found to affect the extent of the Eberlin reaction by either favoring

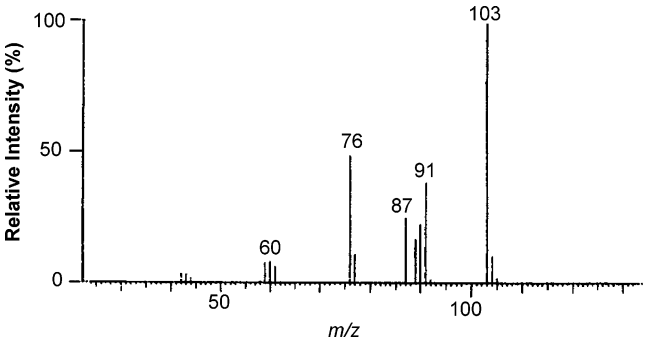


Figure 6. Double-stage MS^2 spectrum showing the dissociation of the acylated oxathiolanes (*m*/*z* 133) into two Eberlin product ions of *m*/*z* 87 and 103. Reprinted with permission from ref 191. Copyright 1994 John Wiley & Sons Limited.

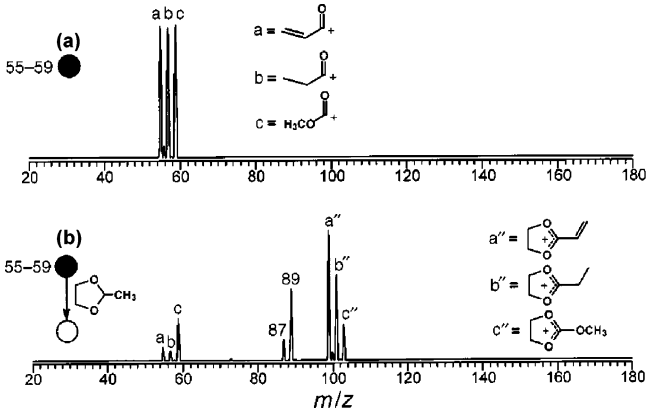


Figure 7. (a) Double-stage MS^2 mass spectrum for an ionic beam consisting of equal amounts of the three acylium ions, $CH_2{=}CH{-}C^+{=}O$ (*m*/*z* 55), $C_2H_5{-}C^+{=}O$ (*m*/*z* 57), and $CH_3O{-}C^+{=}O$ (*m*/*z* 59). Q1 was operated under low resolution to allow simultaneous mass selection of all three ions. No reagent gas was used. (b) Double-stage MS^2 mass spectrum showing products of the simultaneous ion/molecule reactions of these three acylium ions with 2-methyl-1,3-dioxolane. From the yields of the cyclic ionic acetals a″, b″ and c″, the reactivity order is $CH_2{=}CH{-}C^+{=}O > C_2H_5{-}C^+{=}O > CH_3O{-}C^+{=}O$. Reprinted with permission from ref 141. Copyright 1997 Royal Society Chemistry.

or inhibiting the ring-opening process. Charge-stabilizing 2-substituents such as alkyl groups facilitate ring-opening and the overall reaction. The corresponding effect is particularly pronounced for the phenyl group owing to its ability to stabilize the positive charge. Alkyl substituents at the C4-position tend to inhibit the reaction, probably because of steric effects operating on the recyclization step. The 2-methoxy substituent greatly decreases the reaction extent, likely by favoring proton transfer (from the acylium ion to the acetal) or CH_3O^- abstraction (by the acylium ion).

Competition experiments have been used to measure the relative reactivity of acylium ions toward cyclic acetals.[141] For instance, by mass-selection of three acylium ions of similar *m*/*z*, that is, $CH_2{=}CH{-}C^+{=}O$ of *m*/*z* 55, $C_2H_5{-}C^+{=}O$ of *m*/*z* 57, and $CH_3O{-}C^+{=}O$ of *m*/*z* 59, and simultaneously reacting them with 2-methyl-1,3-dioxolane (Figure 7), the order of reactivity was determined to be $CH_2{=}CH{-}C^+{=}O > C_2H_5{-}C^+{=}O > CH_3O{-}C^+{=}O$. Therefore, it appears that alkoxy substituents on acylium ions decrease reactivity toward Eberlin reactions, whereas substituents of the α,β-unsaturated type such as the vinyl group (and the phenyl group) favor the reaction.

Eberlin reactions also occur readily for monothio cyclic acetals such as 2-methyl-1,3-oxathiolane (Figure 8a) and 1,3-

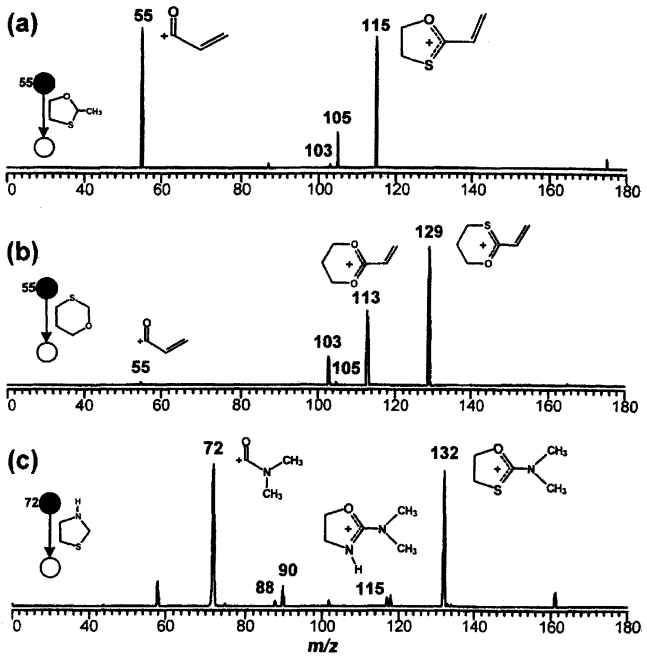


Figure 8. Double-stage MS^2 mass spectra showing products of the ion/molecule reactions of acylium ions with (a) 2-methyl-1,3-oxathiolane, (b) 1,3-oxathiane, and (c) thiazolidine. Note that cyclic ionic thioketals are the dominant or nearly exclusive products. Reprinted with permission from ref 190. Copyright 1997 American Chemical Society.

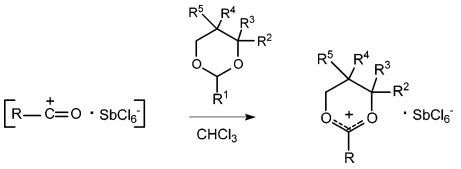
oxathiane (Figure 8b) in reactions with the α,β-unsaturated acylium ion $CH_2{=}CH{-}C^+{=}O$ of *m*/*z* 55. Thiazolidine, a sulfur−nitrogen cyclic acetal, also reacts extensively with the acylium ion $(CH_3)_2{-}N{-}CO^+$ via Eberlin polar transacetalization (Figure 8c). Regioselectivity is pronounced as the relative yields of the cyclic ionic acetals and cyclic ionic thioacetals show that the initial acylation occurs almost exclusively (Figure 8a) or predominantly (Figure 8b,c) at the sulfur atom to produce oxathiolanylium or oxathioanium ions. Note the unique spectra of each isomeric sulfur acetal (Figure 8a,b), which permits their unequivocal identification based on distinctive bimolecular reactivity. Similar regioselectivity with great preference for initial electrophilic attack at the sulfur atom has been observed for other O/S/NH-mixed cyclic acetals (see below).

3.3. Relationship to Condensed-Phase Reactions

Acylium ions, because of their relative ease of preparation, constitute a common and synthetically useful class of stable carbocations in the condensed phase. They are available in the form of acylium ion salts or are formed in situ mainly from carboxylic acid halides.[192] Acylium ions participate as key ionic reaction intermediates in the classical Friedel−Crafts acylation reactions[137] and have been used in the syntheses of a variety of heterocyclic systems such as tris-(3,4,5,6-tetrahydro-1,3,5-triazinium) and tris(1,3,5-oxadiazinium) salts.[193,194] In the dilute gas-phase environment of the mass spectrometer, a variety of long-lived solvent- and counterion-free acylium ions have been generated, isolated, and reacted, and a rich gas-phase chemistry has been observed for such gaseous ions. Eberlin reactions of acylium ions occur by routes that are similar to the condensed-phase acetalization and transacetalization reactions. Interestingly, the direct polar transacetalization of acylium ions occurs in solution; it was reported that a reaction involving solvated

acylium ions (formed from carboxylic acid chlorides in the presence of antimony pentachloride, a super-strong Lewis acid) and neutral 1,3-dioxanes generates 1,3-dioxanium hexachloroantimonate salts in 25−95% yield (Scheme 6).[140]

Scheme 6



Likewise, the cycloaddition of 1,3-diols with solvated acylium ions in CH_2Cl_2 was reported to give 12−97% yield of 1,3-dioxanium hexachloroantimonate salts.[195] These reactions in solution might now be classified as analogues of the Eberlin type.

These reports open prospects for the broader application of the Eberlin reaction in solution. Because the gas-phase Eberlin reaction has been extended to a variety of gaseous amphoteric cations, it is likely that polar acetalization or transacetalization reactions of some amphoteric cations can occur in solution under appropriate conditions. Acylium ions are natural candidates, but other long-lived solution ions such as the phenylnitrenium ion, $PhNH^+$,[196] might also be successful. Because polar transacetalization in solution can be either favored or inhibited by solvation and/or by ion pairing, particular Eberlin reactions performed in both phases might provide further information on relationships between gas-phase and condensed-phase chemistry.

3.4. Related Ion/Molecule Reactions

A number of gas-phase reactions related to Eberlin reactions have been reported, perhaps the closest being the *gas-phase Meerwein reaction.*[197] This gas-phase bimolecular reaction is analogous to the condensed-phase reaction described in 1955 by Meerwein.[198] It occurs via three-to-five-membered ring expansion of epoxides or thioepoxides and is promoted by gaseous acylium or thioacylium ions (Figure 9). Ab initio calculations, ^{18}O-labeling, and MS^3 pentaquadrupole experiments demonstrate that the reaction proceeds via a mechanism (Scheme 7) analogous to that of the Eberlin polar transacetalization (Scheme 2). Initially, O(S)-acylation of the (thio)epoxide occurs and is followed by rapid ring opening, and the ring closure is promoted by intramolecular nucleophilic O-attack by the carbonyl group. These steps result in three-to-five-membered ring expansion,

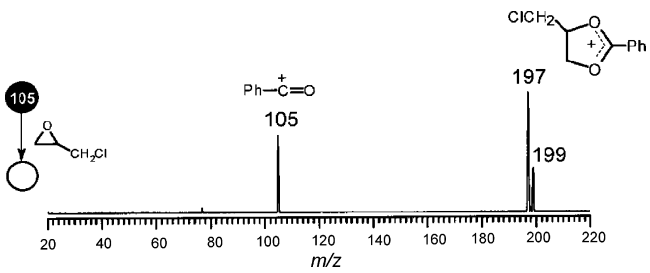
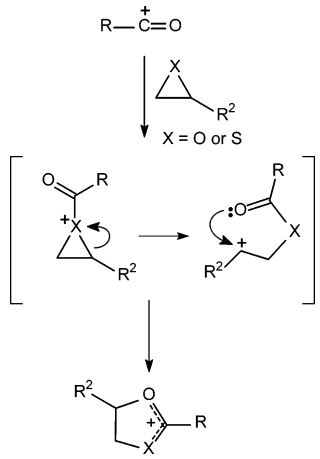


Figure 9. Double-stage MS^2 mass spectrum showing products of the ion/molecule reaction of the acylium ion $PhC^+{=}O$ of *m*/*z* 105 with epichlorohydrin. Note that the pair of isotopologue Meerwein product ions (cyclic ionic acetal) of *m*/*z* 197 and 199 dominate the spectrum. Reprinted with permission from ref 197. Copyright 2000 Wiley-VCH Verlag GmbH.

Scheme 7

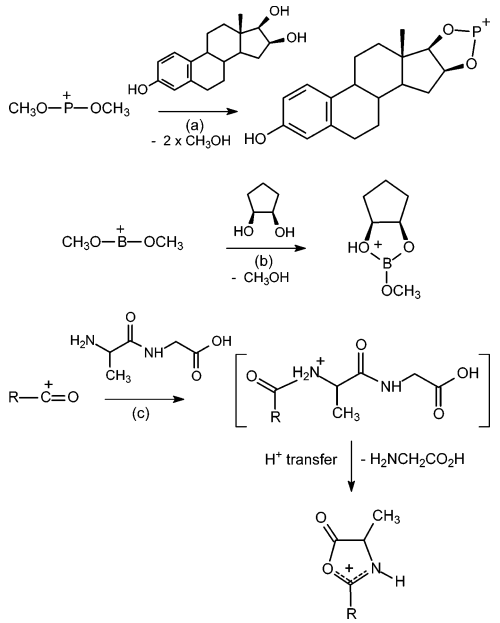


and the reaction yields cyclic ionic acetals: 1,3-dioxolanylium ions or 1,3-oxathiolanylium ions.

The Eberlin and Meerwein reactions display many common features. Both reactions form the same class of product ions. Mechanistically, both reactions are quite similar with only two small differences: (i) in the ring opening step, the Meerwein reaction proceeds via an unstabilized carbocation whereas in the Eberlin reaction this step proceeds with anchimeric assistance from the neighboring heteroatom thus forming a more stable ion; (ii) the ring closure step in Eberlin reactions involves release of a carbonyl compound whereas there is no leaving group during the intramolecular nucleophilic attack in the Meerwein reaction. Both reactions are also thermodynamically highly favorable, dominating the product distribution or even occurring exclusively. Also for both reactions, proton transfer and hydride abstraction are the main competing reactions, particularly for the more basic neutral reactants and the more acidic (thio)acylium ions. When (thio)epoxides or (thio)acetals react with acylium ions, both reactions promote O(S)-scrambling; when epoxides or cyclic acetals react with thioacylium ions and the adducts are dissociated, both reactions promote S/O replacement. A related Meerwein reaction involves trimethylene oxide reaction with acylium and thioacylium ions with four-to-six-membered ring expansion (note the analogy with Eberlin reactions with 1,3-dioxanes, Scheme 2 for $n = 2$).[197] Because of the close analogy, most amphoteric gaseous ions that have been observed to undergo Eberlin reactions should also react efficiently by Meerwein reactions, as recently observed in the particular case of phosphonium ions.[199]

Another gas-phase reaction closely related to the Eberlin reaction is that of the phosphenium ion, $P(OCH_3)_2^+$, with cyclic vicinal diols to form cyclic phosphenium ions. This P-centered ion reacts via polar acetalization in a stereoselective reaction, which has been applied to the gas-phase differentiation of cis and trans isomeric steroids (Scheme 8a).[200] As shown in Figure 10, in a FT-ICR reaction cell a diagnostic cyclic product ion of *m*/*z* 317 was observed in the reaction of the dimethoxyphosphenium ion of *m*/*z* 93 with *cis*-estriol rather than *trans*-estriol through the loss of two molecules of methanol.[200] Similarly, the analogous B-centered ion was also found to react with vicinal diols by an acetalization-like mechanism (Scheme 8b), and this reaction has been proposed as a method for the differentiation of stereoisomeric diols.[201] Acylium ions were also found to react with a neutral dipeptide (alanylglycine) via an acetalization-like mechanism involving N-terminal derivatization

Scheme 8



and fragmentation to form a "ionic acetal" (Scheme 8c), that is, a modified b_1 ion, which is typically not observed in the fragmentation of protonated peptides.[134]

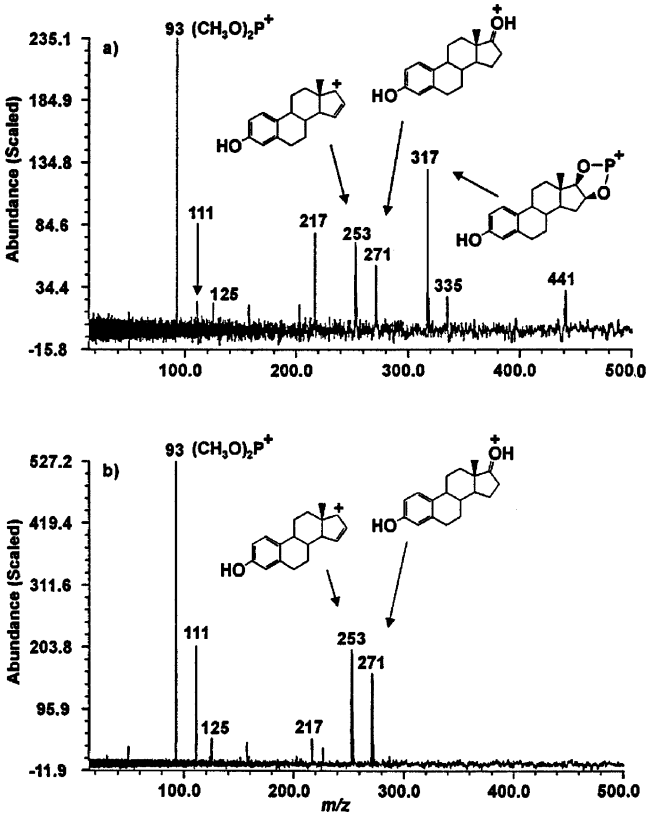


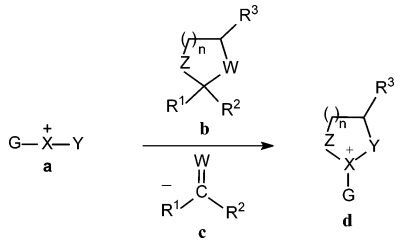
Figure 10. FT-ICR mass spectra (a) measured after 20 s reaction between the dimethoxyphosphenium ion of *m*/*z* 93 and 1,3,5(10)-estratriene-3,16α,17α-triol (*cis*-estriol), which yields a diagnostic cyclic product ion of *m*/*z* 317 through the loss of two molecules of methanol and (b) measured after 15 s reaction between the dimethoxyphosphenium ion of *m*/*z* 93 and 1,3,5(10)-estratriene-3,16α,17*β*-triol (*trans*-estriol). Note that no ion of *m*/*z* 317 is formed. Reprinted with permission from ref 200. Copyright 2002 Elsevier.

4. Scope of the Eberlin Reaction

The Eberlin reaction is general for a variety of reactant ions and cyclic neutral acetals. Any reactant ion with a Lewis acid site able to participate in electrophilic addition and a Lewis basic site able to effect nucleophilic ring-closure is in principle eligible to undergo the Eberlin reaction. Indeed, the reaction has been observed not only for acylium ions ($R-C^+=O$) but also for many other amphoteric ions such as thioacylium ($R-C^+=S$),[139,141] carboxonium ($H_2C=O^+-R$),[142] carbosulfonium ($H_2C=S^+-R$),[142] distonic or distonoid radical acylium ($^\bullet R-C^+=O$, R = alkyl, allyl, or phenyl),[143,144] diacylium ($O=C=N^+=C=O$),[145,146] sulfinyl ($R-S^+=O$),[141,147] arylsulfenium (ArS^+),[148] borinium ($(RO)_2B^+$),[149] silylium ($(RO)_3Si^+$),[150] phosphonium ($R_2P^+=O$),[150,151] arylnitrenium ($ArNH^+$),[152] nitronium (NO_2^+)[153] and hetarynium ions (2-pyridyl, 2-pyrrolyl cations, and their analogues).[154]

The Eberlin reaction has been generalized to a considerable extent, and both Scheme 9 and Table 1 summarize this

Scheme 9



diversity. Reactant ions in Eberlin reactions can be depicted by the general formula GX^+Y (**a**). Electrophilic attack by the Lewis acidic site X in ion **a** upon neutral reagent **b** leads to ring opening and is followed by nucleophilic ring closure promoted by the Lewis basic site Y, which releases the neutral carbonyl compound **c** and forms the final cyclic ionic acetal **d** (Scheme 9).

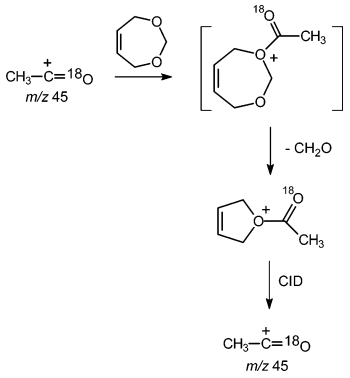
The neutral reactants **b** in Eberlin transacetalization type reactions can include five-, six-, and seven-membered 1,3-O,O-heterocycles ($n = 1-3$) and their mono-sulfur and nitrogen analogues. Note that for seven-membered heterocycles, Eberlin reactions normally compete with ring contraction reactions (see below). Formally, the Eberlin reaction produces a replacement of the group $(R^1R^2)C-W$ by $(G)-X^+-Y$ in a cyclic system.

Some characteristics are common to Eberlin reactions: (i) Yields are influenced by substituents and by the ring and chain sizes of the neutral reactants, for instance, 2-phenyl-substituted cyclic acetals are more reactive than non-2-substituted acetals. (ii) The cyclic ionic acetal products often fragment back to the original reactant ions upon CID, but ring substituents, heteroatoms on the ring, and the ring size can greatly influence dissociation behavior, facilitating other more characteristic dissociation pathways.[141,147,149] (iii) Ring contraction or expansion can accompany the Eberlin reaction, and ^{18}O labeling has been shown to allow monitoring of the relative extents of both processes. For example, a less exothermic but more kinetically favored reaction, seven-to-five-membered ring contraction, dominates over polar transacetalization in the reaction of $(CH_3)_2NC^+=O$ (the most reactive acylium ion so far tested in Eberlin reactions) with 1,3-dioxepane and 1,3-dioxep-5-ene (Scheme 10).[202] Similarly, five-to-four-membered ring contraction was observed in the Eberlin reaction of arenesulfenylium cations.[148] Five-to-six-membered ring expansion occurs, however, in Eberlin

Table 1. Summary of Eberlin Reactions as Outlined in Scheme 9

n	G, R^1, R^2	X	Y	W, Z	Comments	Ref.
1	R^1, R^2 = H, CH_3; G = Alkyl, Ph, OH, OCH_3, $NHCH_3$, $N(CH_3)_2$, Cl, $CH=CH_2$, N=CHPh, $CH=C(OH)CH_3$	C	=O(S)	O, O	Prototype reaction	139
1-3	R^1, R^2 =H, CH_3, OCH_3, C_2H_5; G = $CH=CH_2$, $N(CH_3)_2$, C_2H_5	C	=O	1) O, O; 2) O, S; 3) S, NH.	Application: differentiation of isomers	190
1, 2	R^1, R^2 = H, CH_3; G = $CH=CH_2$, CH_3, C_2H_5, $(CH_3)_2N$, CH_3O, Cl, Ph	C, S	=O(S)	O, O	Ion structural studies	141
1	R^1, R^2 = H, CH_3, Ph; G= H, H	C	$-O(S)CH_3$	O, O	Eberlin reactions of carboxonium and carbosulfonium ions	142
3	R^1, R^2 = H, CH_3, Ph; G = CH_3, $N(CH_3)_2$	C	=O	O, O	Seven- to five- membered ring contraction	202
1	R^1, R^2 = H, CH_3, Ph; G = $-C_4H_4-$, $-NC_3H_3-$	C	=N-	O, O	Eberlin reactions of hetarynium ions	154
1	R^1, R^2 = H, CH_3, Ph; G = alkyl, allyl or phenyl radical	C	=O	O, O	Eberlin reactions of distonic acylium ions	143,144
1, 2	R^1, R^2= H, CH_3, C_2H_5; G = NCO(S), CHCO, CNO	C	=O(S)	O, O	Double transacetalization	145,146
1, 2	R^1, R^2 = H, CH_3; G = $-C_4H_4-$	C	-C=NH	O, O	Eberlin reactions of phenylnitrenium ions	152
1	R^1, R^2 = H, CH_3; G= CH_3, Ph, Cl, OCH_3, OC_2H_5	S	=O	O,O	Distinguishing sulfinyl cation from its isomers	147
1, 2	R^1, R^2 = H, CH_3, Ph; G= Ph	S	None	O, O	Ring contraction and cycloreversion	148
1, 2	R^1, R^2 = H, CH_3, Ph; G = CH_3, OCH_3	B	$-OCH_3$	1) O, O 2) N, S	Eberlin reactions of borinium ions	149
1, 2	R^1, R^2 = H, CH_3, Ph; G = $N(CH_3)_2$	B	$-NMe_2$	1) O, O 2) N, S	Synthesis of B,N,O-containing heterocycles	234
1, 2	R^1, R^2 = H, CH_3, OCH_3, Ph; G = CH_3, OCH_3	Si	$-OCH_3$	1) O, O 2) N, S 3) O, S	Eberlin reactions of silylium ions	150
1, 2	R^1, R^2 = H, CH_3, Ph; G = CH_3, OCH_3	P	=O	1) O, O 2) N, S	Eberlin reactions of phosphonium ions	149,151
1	R^1, R^2 =H, CH_3; G = O	N	=O	O, O	Eberlin reactions of nitronium ions	153

Scheme 10



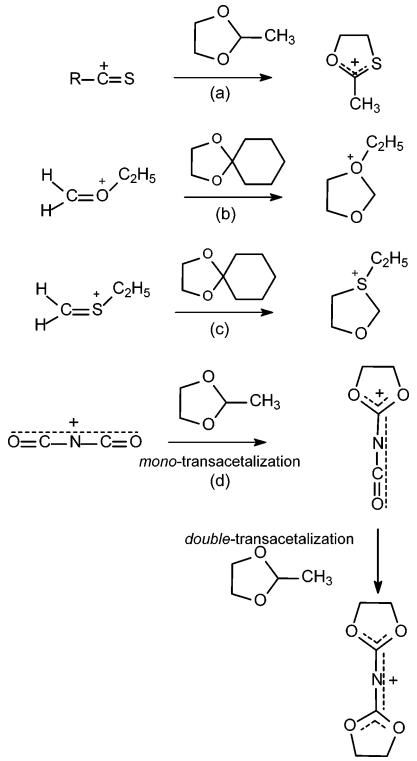
reactions of phenylnitrenium ions with 2,2-dimethyl-1,3-dioxolane yielding protonated benzomorpholine.[152] (iv) Proton transfer and hydride abstraction are the major side reactions that compete with and can suppress polar acetalization or transacetalization.

4.1. Carboxonium Ions and Related Reagents

Ions closely related to the acylium ion ($R-C^+=O$) also undergo Eberlin reaction. They include thioacylium ($R-C^+=S$, Scheme 11a),[139,141] carboxonium ($H_2C=O^+-R$, Scheme 11b),[142] and carbosulfonium ($H_2C=S^+-R$, Scheme 11c),[142] which react in the gas phase with cyclic acetals by polar transacetalization to form the corresponding cyclic ionic acetals. As in the prototype reaction, Eberlin reactions of these acylium ion variants are initiated by adduct formation through O(or S)-acylation (or alkylation in the case of carboxonium and carbosulfonium) and subsequently proceed by ring opening and recyclization via intramolecular displacement of the carbonyl compound previously protected in its cyclic acetal form. Competition experiments indicate that carbosulfonium ions are much more reactive than carboxonium ions in polar transacetalization. Furthermore, for the simplest six-membered cyclic carboxonium ions, acyclic secondary and tertiary carboxonium ions bearing acidic α-hydrogens, little or no polar transacetalization occurs and proton transfer dominates. This structure-dependent reactivity can be used to distinguish primary from both secondary and tertiary ions.

1,2-Diacetals have long been known for their specific applications in organic synthesis.[203] They can be prepared by the reaction of simple diones with vicinal diols in acidic solution.[204] In the gas phase, an interesting double polar transacetalization of *singly charged* diacylium ions of the

Scheme 11

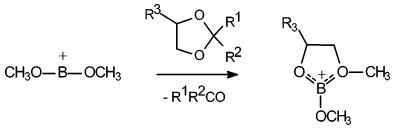


O=C=X$^+$=C=O type (X = N, CH) with cyclic acetals has been reported.[145,146] The reaction is exothermic and highly efficient and forms a new type of highly charge-delocalized ion, an *ionic diacetal* (Scheme 11d). In the case of the reaction of O=C=N$^+$=C=O with 2-methyl-1,3-dioxolane, ab initio calculations show that mono-transacetalization is exothermic by 33.3 kcal/mol, while the double transacetalization is 43.1 kcal/mol exothermic.[145] Low-energy CID of the cyclic ionic diacetals of O=C=N$^+$=C=O and O=C=CH−C$^+$=O sequentially frees each of the protected acylium sites to form first the mono-derivatized ions and then the fully deprotected singly charged diacylium ion. With cyclic acetals, the singly charged acylium−thioacylium ion O=C=N$^+$=C=S reacts promptly and selectively by mono-transacetalization at its acylium site, but the free thioacylium site of the resulting cyclic ionic acetal is nearly unreactive toward a second polar transacetalization step. One concludes that only the acylium site and not the thioacylium site of O=C=N$^+$=C=S can be efficiently derivatized by polar transacetalization (or selectively protected in the gas phase).

4.2. Borinium Ions

Eberlin reactions of dicoordinated borinium ions, $(RO)_2B^+$ and $R_1OBR_2^+$, with neutral acetals and thiazolidine follow the classical reaction mechanism (Scheme 2) and yield tricoordinated cyclic boron cations (Scheme 12).[149] Reactions

Scheme 12

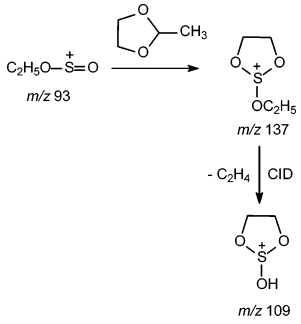


of such ions closely resemble polar transacetalization of acylium ions, and the cyclic structure of the tricoordinated boron cation has been proven by the distinctive dissociation behavior when compared to its acyclic isomeric ions and by CID comparison with the authentic cyclic tricoordinated boron cation. The five-membered cyclic boron cations dissociate by loss of ethylene oxide to re-form the reactant dicoordinated borinium ion, but the six-membered boron cations behave differently in that they fragment via ethylene loss. Consistent with the proposed mechanism, the efficiency of the ion/molecule reaction falls in the order $CH_3OB^+C_2H_5 > CH_3OB^+OCH_3 \gg CH_3B^+CH_3$. This order shows that the higher the nucleophilicity of the borinium ion, the greater the reaction efficiency. Furthermore, the oxygen atom in the reactant boron cation plays an essential role in polar transacetalization because the oxygen lone pair participates in the nucleophilic ring reformation step. Such a step is not only expected to be rate-limiting but also expected to determine the structure of the final product ion. The reaction exothermicity and regioselectivity are controlled by both the Lewis acidity of the reactant ions and the leaving ability of the released neutrals in the rate-limiting nucleophilic-induced recyclization step.

4.3. Sulfinyl Ions and Arylsulfenium Ions

Sulfinyl ions represent an important class of closed-shell sulfur species, which remain unknown in solution. Gaseous sulfinyl cations are common, however, and many of them, R−S$^+$=O (R = CH_3, Ph, Cl, OCH_3, OC_2H_5), have been found to undergo the Eberlin reaction with the cyclic acetal, 2-methyl-1,3-dioxolane.[141,147] Polar transacetalization reactivity and simple dissociation of the products that in turn re-form the original reactant ions are among the initial lines of evidence collected to establish sulfinyl cations as stable gas-phase species.[147] Isomeric ions such as S=O$^+$−Ph and CH_2=S$^+$−OH fail to share this reactivity. An interesting exception to the characteristic regeneration of the precursor ion upon dissociation is loss of ethylene from the Eberlin product ion of $C_2H_5O-S^+=O$ (Scheme 13), suggestive of the covalently

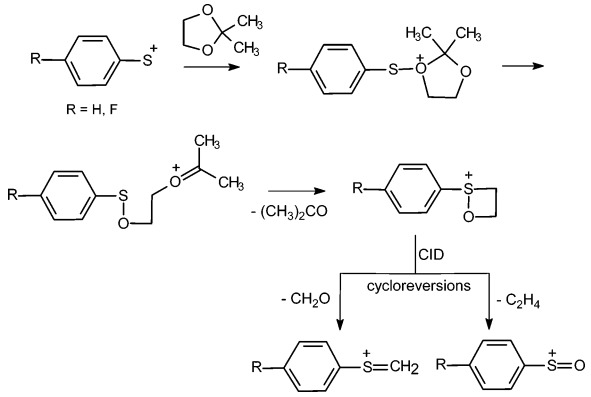
Scheme 13



bound cyclic nature of the product. An additional interesting phenomenon is that sulfinyl cations show quite diverse reactivity toward 1,3-dioxane, the higher homologue of the usual dioxolane reagent. The α,β-unsaturated sulfinyl cation $CH_2=CH-S^+=O$ is considerably more reactive than $CH_3-S^+=O$, whereas Ph-S$^+$=O, Cl−S$^+$=O, and the alkoxy-substituted sulfinyl cation $CH_3O-S^+=O$ are all inert toward 1,3-dioxane.[141]

Scheme 14 generalizes one extreme case of the Eberlin

Scheme 14



reaction involving the arenesulfenylium cations ArS^+ in which X = S and Y is absent (X and Y are defined in Scheme 9).[148] Molecular orbital calculations reveal that the positive charge of ArS^+ ions is preferentially located at the sulfur atom rather than at the para- and ortho-positions of the phenyl group.[205] Experimental studies on the gas-phase reactivity of PhS^+ toward ethylene, carbon monoxide, and nitrogen nucleophiles suggest that addition occurs at the sulfur atom.[206] In the Eberlin reaction, PhS^+ (generated by EI of thioanisole) shows amphiphilic character by displaying both electrophilic addition and intermolecular nucleophilic substitution. As Scheme 14 shows, PhS^+ acts as an electrophile in the initial addition and ring-opening steps, and after the formal charge site shifts, the sulfur center acts as a nucleophile assisting in the recyclization step. Net replacement of C−O by S$^+$ yields a characteristic product via a ring contraction process; that is, it gives the 2-phenyl-1,2-

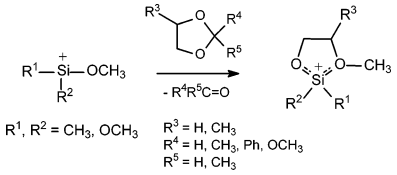
oxathietan-2-ium ion, which dissociates upon CID into $PhS^+{=}CH_2$ or $PhS^+{=}O$.

Substituents at the para-position of the benzene ring are observed to affect the reactivity of arenesulfenylium ions. Whereas *p*-fluorobenzenesulfenium cation, $p\text{-}F{-}C_6H_4{-}S^+$, displays a similar reactivity to that of PhS^+, no Eberlin product was observed when the electron-donating amino and methoxy substituents were placed at the para-position of the phenyl group. It is likely that these substituents delocalize the positive charge of the arenesulfenium ion making it less electrophilic toward cyclic acetals.

4.4. Silylium Ions

Gas-phase ion/molecule reactions of silicon-containing ions with various coordination numbers, especially the trimethylsilyl cation $(CH_3)_3Si^+$, have drawn much attention,[207,208] for example, in terms of bonding to alcohols, ethers, ketones, and carboxylic acids.[209−213] Eberlin reactions of silylium ions with a series of dioxolanes and with dioxane, thiazolidine, and 1,3-oxazinane generate cyclic tetracoordinated silicon products efficiently (Scheme 15).[150] The reac-

Scheme 15

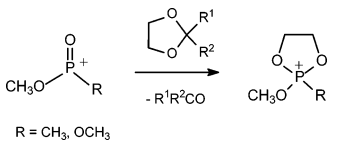


tion follows the classical steps through which C−O (or C−S or C−N) is replaced by Si−O$^+$ in the cyclic acetals or related heterocycles. Competition MS^2 experiments reveal the following reactivity order for silylium ions: $(CH_3O)_3Si^+ > (CH_3O)_2Si^+CH_3 > CH_3OSi^+(CH_3)_2 \gg (CH_3)_3Si^+$. It was found that all the oxygen-substituted silylium cations undergo Eberlin reactions to form the replacement product ion, but $(CH_3)_3Si^+$ fails to react, likely because of the absence of an O-substituent to act as a Lewis base site, an essential component for the intramolecular nucleophilic ring closure that generates the Eberlin product ion. Similar observations were made for borinium ions $(RO)_2B^+$, $R_1OBR_2^+$, and $R_1BR_2^+$. The substituents on the cyclic acetals affect the extent of the Eberlin reaction of the silylium ion as they do in the boron systems.

4.5. Phosphonium Ions

Organophosphorus compounds are used in plasticizers, pharmaceuticals, and pesticides, and as warfare agents. Owing to their wide application, a variety of mass spectrometric techniques including ion/molecule reactions have been suggested for their identification and used to study their gas-phase reactivity.[214−216] It has been found that the phosphonium ions, $RP(O)OCH_3^+$ (R = CH_3, OCH_3), easily generated from EI of organophosphonates, undergo Eberlin reactions with 1,3-dioxolane to form cyclic 1,3,2-dioxaphospholanium ions (Scheme 16),[151] in which net replacement of C−O by

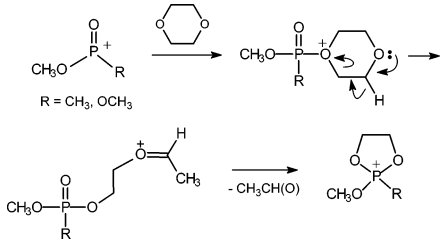
Scheme 16



P−O in the cyclic acetals occurs. 1,3,2-Dioxaphospholane and related oxyphosphoranes are routinely synthesized by condensation of phosphanes and phosphites with diols or diketones in solution,[217] but such a net replacement of C−O by P−O in cyclic acetals through reaction with phosphoryl-containing compounds in solution has not been reported. Because the polarity of the phosphoryl group is greater than that of the carbonyl group, the phosphonium ion is much more easily solvated, and ready solvation is the reason that transacetalization reactivity is masked in the condensed phase. Calculations show that the formation of an initial ion/molecule adduct with strong P−O bonding is the main driving force for the Eberlin reaction of phosphonium ions.[149] Reactions of $RP(O)OCH_3^+$ (R = CH_3, OCH_3) with thiazolidine display a regioselectivity that favors sulfur over nitrogen binding in the first reaction step, the same regioselectivity observed also for acylium ions (section 3.2). When 1,3-oxathiolane is employed, Eberlin product ions result exclusively from initial sulfur binding.

The same two phosphonium ions, $RP(O)OCH_3^+$ (R = CH_3, OCH_3), also undergo Eberlin reactions with 1,4-dioxane to form cyclic 1,3,2-dioxaphospholanium ions.[218] This variant of the Eberlin reaction follows a different mechanism (Scheme 17) from that normally observed (Scheme 2), but

Scheme 17



it forms similar cyclic ionic acetals as does the classic Eberlin transacetalization reaction with 1,3-dioxolane and 1,3-dioxane. The structure of the cyclic product acetal ions was supported by tandem mass spectrometry and by data taken using deuterated 1,4-dioxane-d_8. By contrast, many other types of amphoteric ions such as acylium ions $R'CO^+$ (R′ = CH_3, OCH_3, $N(CH_3)_2$, and Ph), iminium ions $H_2C{=}NHC_2H_5^+$, and carbosulfonium ions $H_2C{=}SC_2H_5^+$ are unreactive toward 1,4-dioxane under the same conditions.

4.6. Arylnitrenium Ions

Nitrenium ions $RR'N^+$, a family of reactive intermediates characterized by a divalent nitrogen having a formal positive charge, are involved in a variety of organic reactions with nucleophiles such as intramolecular addition to carbon−carbon double bonds,[219] and they have also been implicated as the ultimate carcinogens produced from aromatic amine metabolism.[220] The phenylnitrenium ion $PhNH^+$, the analogue of the phenylsulfenium ion PhS^+, can be formed via the reduction of nitrobenzene with vinyl halide radical cation $CH_2{=}CH{-}X^{+\bullet}$ (X = Cl, Br).[221] This reaction occurs in the CI (chemical ionization) ion source of a mass spectrometer and involves a change in formal oxidation number of the nitrogen atom from +3 to −1. Eberlin reactions of $PhNH^+$ with 2,2-dimethyl-1,3-dioxolanes yield a characteristic heterocyclic product ion, protonated benzomorpholine.[152] Figure 11 shows the product ion mass spectrum for the ion/molecule reactions between the phenylnitrenium ion $PhNH^+$ (*m*/*z* 92) and 2,2-dimethyl-1,3-dioxolane. A major Eberlin product ion

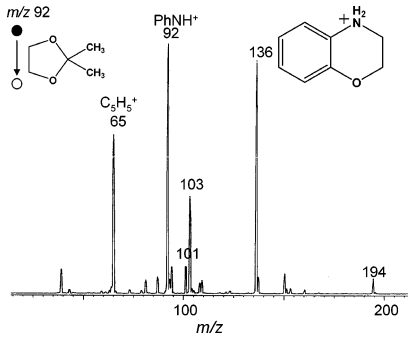
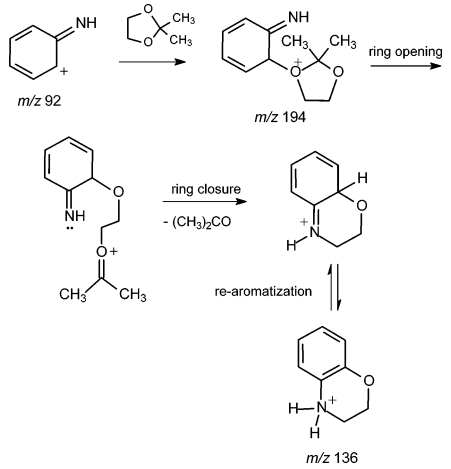


Figure 11. Double-stage MS^2 mass spectrum showing products of the ion/molecule reaction of the phenylnitrenium ion, $PhNH^+$, of *m*/*z* 92 with 2,2-dimethyl-1,3-dioxolane. Reprinted with permission from ref 152. Copyright 2004 Elsevier.

of *m*/*z* 136 is formed by an increase in mass of 44 units. Scheme 18 depicts the proposed mechanism for Eberlin

Scheme 18

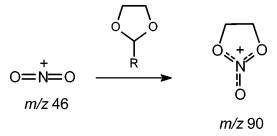


reaction. Initially, the intact adduct of *m*/*z* 194 (Figure 11) is formed. It is proposed that electrophilic addition occurs at the ortho-carbon in the aromatic ring rather than at the nitrogen of the phenylnitrenium ion because of the significant iminocyclohexadienyl cation character of phenylnitrenium ions.[222] Subsequently, ring opening is followed by recyclization with the release of neutral acetone and rearomatization via a 1,3-H shift to yield the final product ion, that is, the protonated *N*-heterocycle benzomorpholine. Overall, the reaction involves five-to-six-membered ring expansion in going from the neutral acetal to the final ionic product, a process with a total exothermicity of 54.7 kcal/mol as calculated by density functional theory (DFT) at B3LYP/6-31G(d) level. Evidence for the structure assignment just noted is from theoretical calculations and from the similar dissociation behavior compared with the authentic ion generated by the protonation of benzomorpholine. This one-step gas-phase synthesis of benzomorpholine is a very concise procedure which suggests a new method to construct the morpholine ring using the phenylnitrenium ion in aqueous solution in which it is long-lived.[196] The observation of indole derivative formation from arylnitrenium ions reacting with ethyl vinyl ether in solution has been reported.[223]

4.7. Nitronium Ion

The solvated nitronium ion, NO_2^+, is the classical reactive intermediate in the condensed-phase nitration of many aromatic substrates.[224] The ion is not stable enough to exist under normal conditions but is created in situ by mixing sulfuric acid and nitric acid or in the form of ionic salts such as nitronium tetrafluoroborate $NO_2^+ \cdot BF_4^-$.[225] Gaseous NO_2^+ is, however, long-lived, and its gas-phase chemistry has been the subject of several studies.[226,227] The nitronium ion displays the desired amphoteric acid−base Lewis properties required for it to undergo Eberlin reactions, and these reactions have been observed with cyclic acetals (Scheme 19).[153]

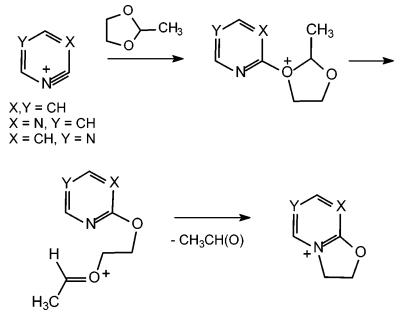
Scheme 19



4.8. Hetarynium Ions

2-Pyridyl and 2-pyrimidyl cations display strong hetarynium (aza-*ortho*-benzynium) ion character[228] and react readily by polar transacetalization with 2-methyl-1,3-dioxolane.[154] This pronounced reactivity results likely from activation of the charge site by the adjacent N-heteroatom (Scheme 20).

Scheme 20



This highly favored reaction is exemplified by the 2-pyrimidyl cation (X = N, Y = CH) of *m*/*z* 79 in Figure 12a. Note the dominant cyclic ionic product of *m*/*z* 123, the dihydrooxazolopyrimidyl cation, and the products of *m*/*z* 89 and 73 arising from the competitive proton transfer and methyl anion (CH_3^-) abstraction reactions, respectively. Interestingly, 4-pyrimidyl and 5-pyrimidyl cations do not react by the transacetalization-like mechanism (Figure 12b,c). The selective reactivity of the ortho 2-isomer in Eberlin reactions has been used to locate the charge site of the 2-pyrimidyl cation, as well as that of its analogue the 2-pyridyl cation (X, Y = CH) and has been used for configuration assignments of monosubstituted pyridines and pyrimidines (see below). In addition, an analogous Eberlin reaction with 2-methyl-1,3-dioxolane selective to the 2-pyrroryl cation was reported very recently.[229]

4.9. Distonic and Distonoid Acylium Ions

α-Oxoketenes are highly reactive, usually transient, but important building blocks in organic synthesis.[230] The short-lived *O*-quinonoid ketene, a prototype cyclic α-oxoketene, has been the subject of much investigation with many reported attempts at spectral characterization and chemical trapping. The formation of the long-lived radical cation of *O*-quinonoid ketene has been demonstrated in the gas phase, and its bimolecular reactivity has been investigated.[231] The ion of *m*/*z* 120 (Scheme 21) is easily formed by EI of salicylic acid followed by water loss and can be trapped via a series

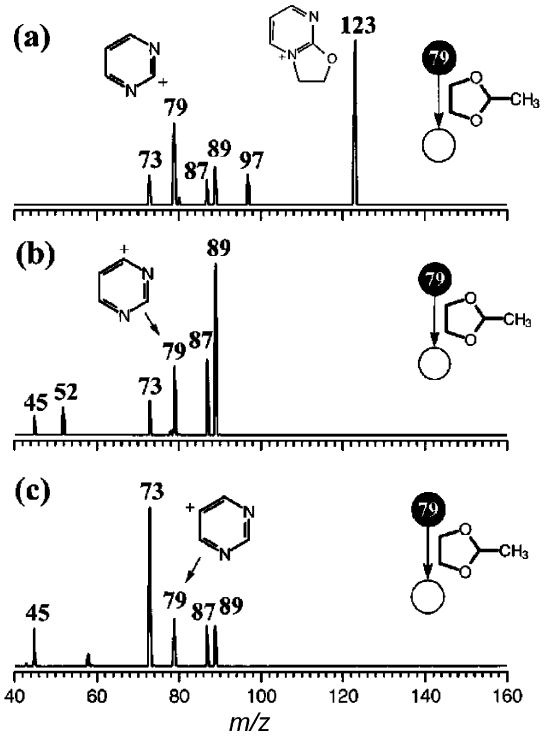
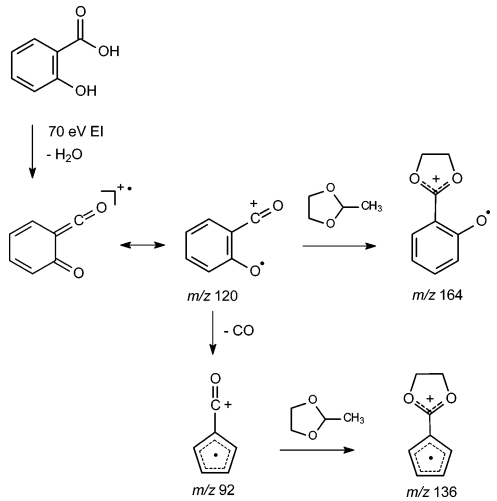


Figure 12. Double-stage MS^2 mass spectra showing products of the ion/molecule reactions of 2-methyl-1,3-dioxolane with the isomeric (a) 2-pyrimidyl cation, (b) 4-pyrimidyl cation, and (c) 5-pyrimidyl cation of *m*/*z* 79. Note in panel a the formation of the Eberlin product ion of *m*/*z* 123 exclusively for the 2-pyrimidyl cation. Reprinted with permission from ref 154. Copyright 1998 Wiley-VCH Verlag GmbH.

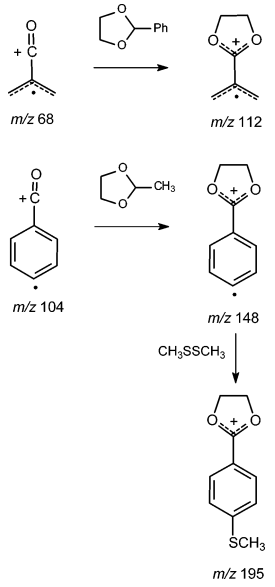
Scheme 21



of very efficient polar [$3^+ + 2$] cycloaddition reactions with enol ethers and ketones. This "distonoid" ion,[232] as well as its fragment ion of *m*/*z* 92, has an electron distribution similar to that of distonic ions with real separation of charge and spin sites. Therefore, both ions are candidates for distonoid acylim ions with dual reactivity (both as ions and as radicals), and their behavior as acylium ions has been probed via Eberlin reactions with 2-methyl-1,3-dioxolane (Scheme 21). Both cations react as simple substituted acylium ions in the Eberlin reactions shown in Scheme 21.

Other gaseous distonic acylium ions including $^{\bullet}CH_2-CH_2-C^+=O$, $^{\bullet}CH_2-CH_2-CH_2-C^+=O$, and $CH_2=C(CH_2^{\bullet})-C^+=O$,[144] as well as the *ortho*-, *meta*-, and *para*-dehydrobenzoyl cations,[143] were found to display dual free radical and acylium ion reactivities. With appropriate neutrals, they react either as acylium ions via the Eberlin reaction with the radical sites remaining inert or as free radicals with inert charge sites by $CH_3S^{\bullet}$ abstraction from dimethyl disulfide (Scheme 22). The Eberlin reaction of distonic acylium ion $CH_2=C(CH_2^{\bullet})-C^+=O$ with 2-phenyl-1,3-dioxolane (Scheme 22), for instance, displays remarkable kinetics forming nearly exclusively the novel distonoid cyclic acetal of *m*/*z* 112 (Figure 13). Hydride abstraction, which yields the minor ion of *m*/*z* 149, is the only side reaction observed. The independence of the charged and radical sites is evident from the fact that after formation of the characteristic Eberlin reaction product, the radical site is available for reaction with the diagnostic dimethyl disulfide reagent to yield the thioanisole product of *m*/*z* 195 (Scheme 22). These particular acylium ions have also been reported to promote ring expansion of epoxides via the gas-phase Meerwein reaction.[197]

Scheme 22



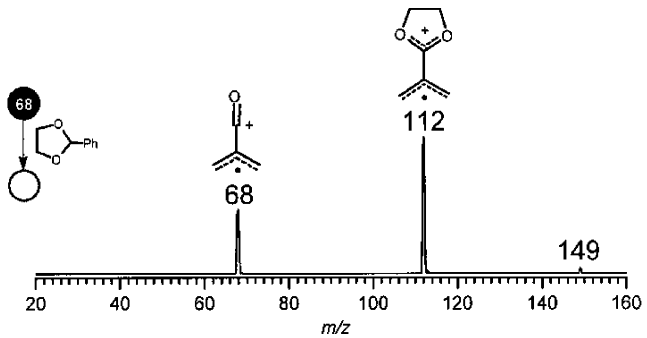


Figure 13. Double-stage MS^2 mass spectrum showing products of the ion/molecule reaction of the allylic distonic acylium ion of *m*/*z* 68 with 2-phenyl-1,3-dioxolane. Note the nearly exclusive formation via the Eberlin reaction of a unique ion: the distonic cyclic ionic acetal of *m*/*z* 112 with an allylic radical site and a 1,3-dioxolanylium ion charge site, both highly stabilized by resonance. The minor ion of *m*/*z* 149 is the hydride abstraction product. Reprinted with permission from ref 144. Copyright 2000 Elsevier.

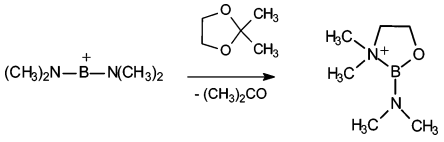
5. Applications

5.1. Gas-Phase Synthesis

5.1.1. Synthesis of Heterocycles

Ion/molecule reactions are sometimes the only known routes to generate elusive chemical species that are not accessible in solution. These species may be ions or neutral molecules. For example, triple heteroatom (B, N, O) ionic heterocycles are potential inhibitors of DNA replication[233] and are easily synthesized in the gas phase via Eberlin reactions using accessible precursors. An example is the gas-phase Eberlin reaction of the dimethylaminoborinium cation $(CH_3)_2NB^+N(CH_3)_2$, generated by EI of tris(dimethylamino)-borane, with 2,2-dimethyl-1,3-dioxolane (Scheme 23).[234] The

Scheme 23



reaction (Figure 14) gives higher yields than the corresponding reactions of the $(CH_3O)_2P^+{=}O$, $(CH_3O)_2B^+$, and $(CH_3O)_3Si^+$ cations. When the relative abundances of Eberlin reaction products for $(CH_3O)_2P^+{=}O$, $(CH_3O)_2B^+$, and $(CH_3O)_3Si^+$ with 2,2-dimethyl-1,3-dioxolane are only 67%, 33%, and 35%, respectively, of the total abundances of the proton transfer and hydride (or alkyl) abstraction products, the reaction of $(CH_3)_2NB^+N(CH_3)_2$ yields an Eberlin product 12 times as abundant as the sum of the proton transfer and hydride (or alkyl) abstraction products. The high Lewis acidity of the borinium ion and the high basicity of the dimethylamino group may facilitate the ring-opening and ring-closure processes, respectively. If the gas-phase chemistry can be transferred to the condensed phase, facile access to the B,N,O-heterocycles may result.

One-step Eberlin reactions of phenylnitrenium ions that readily yield protonated benzomorpholines (Scheme 19) or those of hetarynium ions to yield dihydrooxazolopyridyl or dihydrooxazolopyrimydyl cations may also have indirect

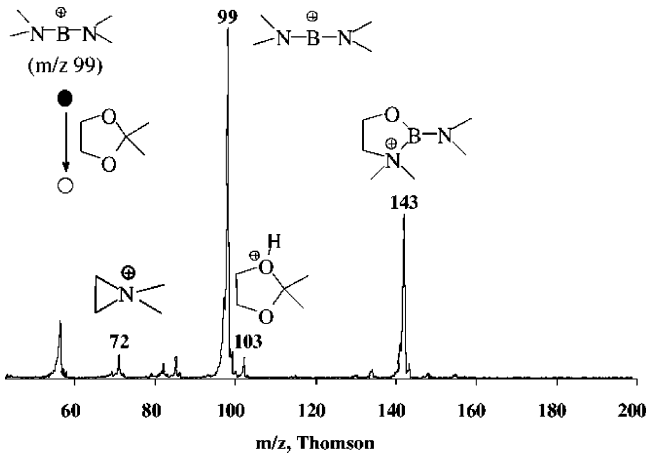


Figure 14. Double-stage MS^2 mass spectrum showing products of the ion/molecule reaction of $(CH_3)_2NB^+N(CH_3)_2$ of *m*/*z* 99 with 2,2-dimethyl-1,3-dioxolane. Note the formation of the Eberlin product ion of *m*/*z* 143, an interesting O,B,N-heterocycle. Reprinted with permission from ref 234. Copyright 2000 John Wiley & Sons Limited.

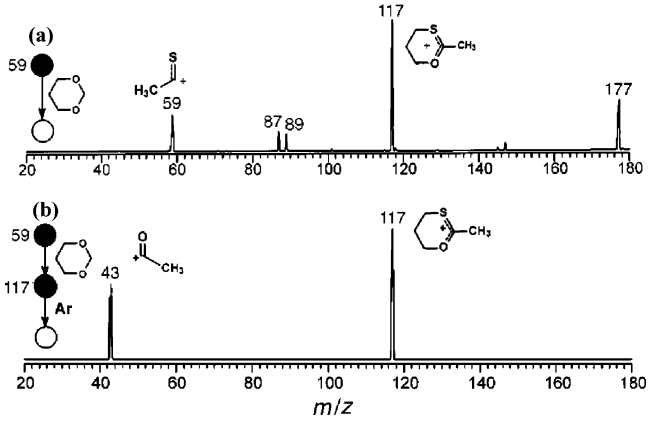


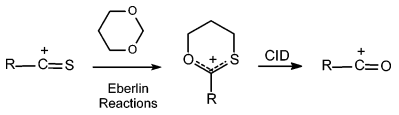
Figure 15. (a) Double-stage MS^2 mass spectrum showing products of the ion/molecule reaction of the thioacylium ion $CH_3{-}C^+{=}S$ of *m*/*z* 59 with 1,3-dioxane; (b) triple-stage MS^3 sequential product mass spectrum showing CID of the Eberlin product ion of *m*/*z* 117. Note that this cyclic ionic thioacetal dissociates exclusively to the oxygen analogue ion $CH_3{-}C^+{=}O$ of *m*/*z* 43. Reprinted with permission from ref 141. Copyright 1997 Royal Society Chemistry.

applications in suggesting viable conventional organic syntheses.

5.1.2. Interconversion of Sulfur and Oxygen Ions

Reaction of $CH_3{-}C^+{=}S$ with 1,3-dioxane[141] followed by CID of the Eberlin product ion (Figure 15) fails to re-form the original reactant ion $CH_3{-}C^+{=}S$. Instead the cyclic ionic thioacetal dissociates to give the oxygen analogue $CH_3{-}C^+{=}O$ (Scheme 24). Because of the relatively poor 2p−3p

Scheme 24



π overlap in multiple bonds between carbon and sulfur, thioacylium ions are anticipated to be less stable than the analogous oxygen acylium ions, which are therefore formed preferentially or exclusively from 1,3-thioxonium ions. The combination of this polar transacetalization reaction with CID therefore provides a unique MS^3 gas-phase strategy to convert thioacylium ions into acylium ions. The same scheme allows one to convert $R_2P^+{=}O$ into $R_2P^+{=}S$, since $R_2P^+{=}S$ can also be obtained via CID of the cyclic phospholanium ion formed by Eberlin reaction of phosphonium ions $R_2P^+{=}O$ with thiazolidine.[151] These examples are indicative of many others that could be developed.

5.2. Isomer Differentiation

5.2.1. Isomeric Ions

The Eberlin reaction can serve as a structurally diagnostic process to differentiate the reactant ion from its isomers. A number of examples have been listed in previous sections. Consider, for instance, the classical set of gaseous isomeric ions of $C_2H_3O^+$ composition (*m*/*z* 43), the acetyl cation $CH_3C^+{=}O$, the O-protonated ketene molecule $CH_2{=}C{=}OH^+$, and the cyclic oxiranyl cation.[139] It was found[139] that upon reactions with 1,3-dioxolane, the acetyl cation readily forms an abundant Eberlin product of *m*/*z* 87, while O-protonated ketene and cyclic oxiranyl cation prefer to yield predominantly the ions of *m*/*z* 73 and 75 via competitive

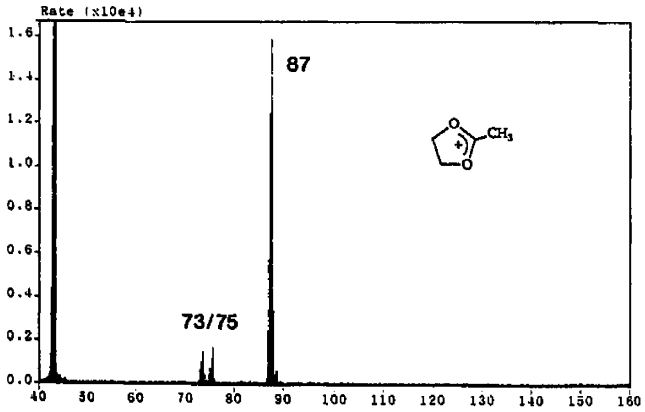


Figure 16. Double-stage MS^2 mass spectrum showing products of the ion/molecule reaction of 1,3-dioxolane with the $C_2H_3O^+$ ion of *m*/*z* 43 formed in a methane/oxygen flame. The Eberlin reaction product is that of *m*/*z* 87, whereas the proton transfer and hydride abstract products are those of *m*/*z* 75 and 73, respectively. Reprinted with permission from ref 235. Copyright 1995 Elsevier.

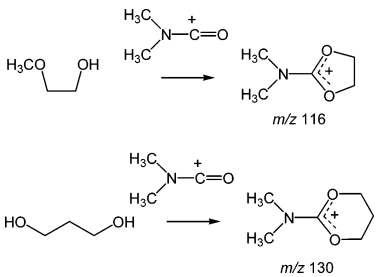
hydride abstraction and protonation of 1,3-dioxolane. Eberlin reactions have therefore been applied by Egsgaard et al. to identify the acetyl cation structure for the $C_2H_3O^+$ ion formed in a methane/oxygen flame based on its reactivity toward 1,3-dioxolane (Figure 16).[235]

Riveros et al. also used Eberlin reactions with ethoxyethanol as chemical probes to recognize acylium ion structures.[236] The fragment ions obtained either from electron ionization of all three methylacetophenone isomers or from thermal dissociation of the methylacetophenone molecular ions were found to retain a benzoyl cation structure, and the cleaved methyl group during the dissociation was determined to be originally attached to the carbonyl group, not to the benzene ring.

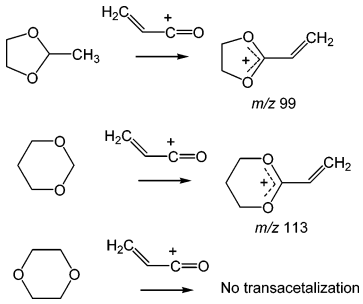
5.2.2. Structural Isomers

The Eberlin and related reactions (Schemes 2 and 3) can be used to identify isomeric neutral compounds. These compounds can be five-, six-, and seven-membered 1,3-O,O-heterocyclic rings and their mono-sulfur/nitrogen analogues, or they can be cyclic/acyclic 1,2-diols, higher homologues, and their sulfur, nitrogen, monoether, and monothioether analogues. The nature of the substituents, ring size, or heteroatom position in cyclic acetals and diols and their analogues not only affects the efficiency of Eberlin reactions but also results in different and chemically characteristic product ions. As shown in Schemes 25 and 26, two groups of structural neutral isomers can easily be differentiated by the Eberlin reactions.[155,190] In addition, the substituent at the 2-position of cyclic acetals is eliminated in the course of the reaction (Scheme 2), while substituents at other ring positions remain in the product, causing corresponding *m*/*z*

Scheme 25



Scheme 26

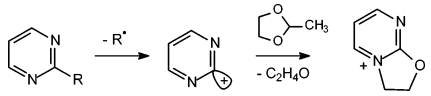


shifts for the cyclic ionic acetals (such as the cases for 2-methyl-1,3-dioxane and 4-methyl-1,3-dioxolane in the Eberlin reactions). A diagnostic method that gives information on the structures of neutral cyclic acetals and diols with respect to substituent positions and ring or chain sizes is therefore available. More importantly, it is likely that more complex synthetically and biologically relevant molecules containing diol, dioxolane, and dioxane can be detected using Eberlin reactions in the future, considering that Eberlin reactions can also be performed under *in-source* ion/molecule reaction conditions using ESI and APCI[158] (see section 5.4) for molecules much heavier and more polar than those employed under the collision cell vacuum conditions so far discussed in this review.

5.2.3. Positional Isomers

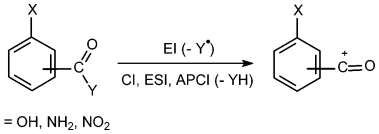
Assignment of positional isomers based solely on mass spectrometry is always challenging and is usually performed indirectly by comparison of the spectra of all possible isomers. An interesting approach for assignment of configuration by MS is to characterize diagnostic fragment ions generated in ways that preserve substituent positional information rather than examining the intact ionized molecule.[154] Monosubstituted pyridines and pyrimidines form pyridyl and pyrimidyl cations (Scheme 20) in which the positional information of the substituent (R) is retained upon R loss because the positive charge remains on localized sp^2 orbitals and H "ring walking" is hampered by relatively high energy barriers. Eberlin reactions with 2-methyl-1,3-dioxolane occur predominantly for the 2-isomer cations (Scheme 27), and they have been shown to distinguish the 2-pyridyl cation from its 3- and 4-isomers.[154]

Scheme 27



Benzoyl cations may also function as structurally diagnostic reagent ions for configuration assignments of the disubstituted nitro, amino, or hydroxyl acylbenzenes.[157] Such ions retain the position information of acyl substituents since the positive charge site is placed, formally, on the CO^+ substituent (Scheme 28). Eberlin reactions with 2-methyl-1,3-dioxolane allow distinction of the *m*-aminobenzoyl cation

Scheme 28



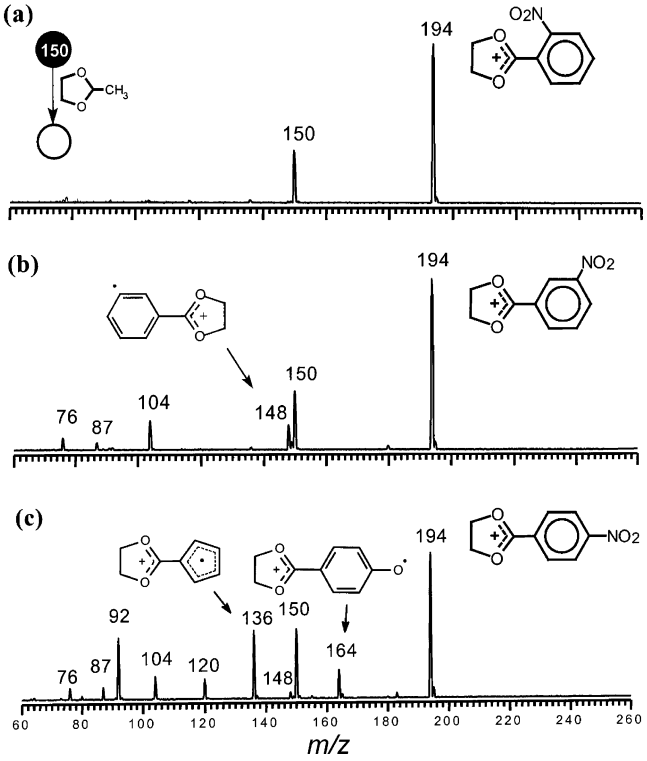
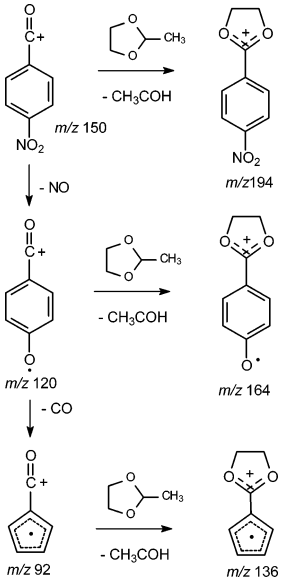


Figure 17. Double-stage MS^2 mass spectra showing products of the ion/molecule reactions of 2-methyl-1,3-dioxolane with isomeric ions of *m*/*z* 150: (a) 2-nitrobenzoyl, (b) 3-nitrobenzoyl, and (c) 4-nitrobenzoyl cations. Note the unique distribution of Eberlin product ions and fragments, which characterize each isomer. Reprinted with permission from ref 157. Copyright 2005 Elsevier.

from its ortho and para isomers and identification of each of the three isomeric 2-, 3-, and 4-nitrobenzoyl cations (Figure 17).[157] Scheme 29 depicts Eberlin reactions of the

Scheme 29



4-nitrobenzoyl cation and its fragments. These ions, including the distonoid fragment ion generated by CO loss, undergo the transacetalization reaction.

5.2.4. Diastereomers

Eberlin polar acetalization has been applied to distinguish cis and trans diastereomers such as those of 1,2-cyclopentanediol and 1,2-diamino cyclohexane (Figure 18). Owing to backside displacement (a configuration diagnostic ion/molecule reaction), the Eberlin reaction is specific to trans diastereomers (Scheme 30).[155]

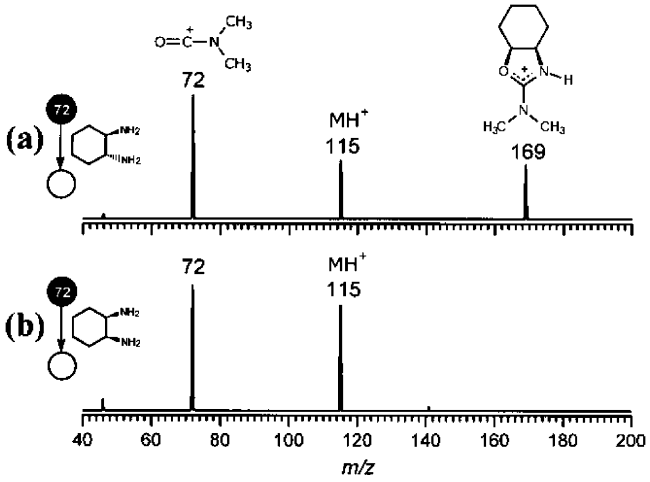
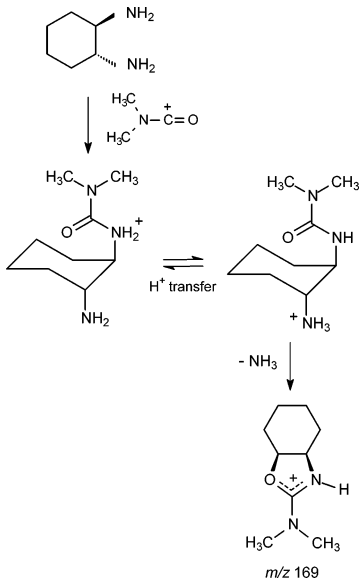


Figure 18. Double-stage MS^2 mass spectra showing products of the ion/molecule reactions of the acylium ion $(CH_3)_2N-C^+=O$ of *m*/*z* 72 with (a) *trans*- and (b) *cis*-1,2-diamino cyclohexane. Eberlin acetalization is diastereoselective occurring only with the trans isomer to form the ion of *m*/*z* 169. The proton-transfer product of *m*/*z* 115 is indicated as MH^+. Reprinted with permission from ref 155. Copyright 2001 Elsevier.

Scheme 30

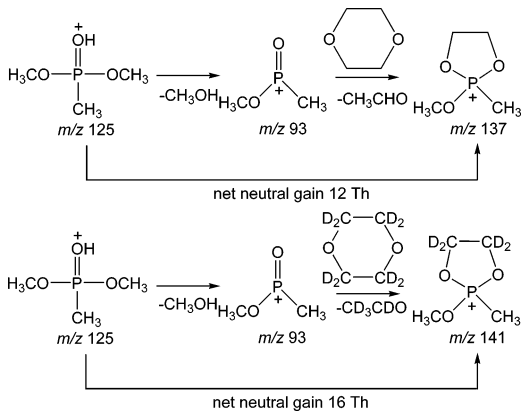


5.3. Highly Selective Trace Organic Analysis

5.3.1. Chemical Warfare Simulants

As noted, amphoteric ions with both Lewis acid and Lewis basic sites are able to undergo the Eberlin reaction. However, when the neutral reactant is 1,4-dioxane instead of a traditional acetal such as 1,3-dioxolane, phosphonium ions $RP(O)OCH_3^+$ ($R = CH_3$, OCH_3) undergo the Eberlin reaction to yield cyclic transacetalization products, 1,3,2-dioxaphospholanium ions (Scheme 17), while many other types of amphoteric ions do not react. The selectivity of this ion/molecule reaction for phosphonium ions has been used to identify the organophosphorus chemical warfare agent simulant dimethyl methylphosphonate (DMMP) in a complex mixture containing ketones, esters, and amides.[218]

Scheme 31



As shown in Scheme 31, when the protonated DMMP ion, $CH_3P(OH)(OCH_3)_2^+$ (*m*/*z* 125), collides with 1,4-dioxane, it forms the fragment ion $CH_3P(O)OCH_3^+$ (*m*/*z* 93), which subsequently reacts to form the product of *m*/*z* 137. During this reaction sequence, there is a net gain of 12 units of *m*/*z* in going from the protonated molecule $CH_3P(OH)(OCH_3)_2^+$ to the product ion. The characteristic and unusual mass shift is 16 units when 1,4-dioxane-d_8 is used as the neutral reagent. Figure 19a shows the complex isobutene chemical ionization mass spectrum of a mixture containing dimethyl-3-pentanone, methyl trimethyl acetate, DMMP, and *N*,*N*-diethyl propionamide, in which the protonated molecules of the four compounds are detected as the ions of *m*/*z* 115, 117, 125, and 130, respectively. When a mixture of 1,4-dioxane and 1,4-dioxane-d_8 is used as the collision gas, only protonated DMMP, $CH_3P(OH)(OCH_3)_2^+$ (*m*/*z* 125), was detected in the specific method of examining reactions with particular mass changes known as the MS^2 neutral gain scan[185,237] when the mass/charge gain was set to either 12 or 16 (the data are shown in Figure 19b,c). The protonated ions of 2-dimethyl-3-pentanone, methyl trimethyl acetate, and *N*,*N*-diethyl propionamide are not observed because neither they nor their fragment ions undergo Eberlin reactions with 1,4-dioxane. It is likely that similar specific Eberlin reactions can be developed for characterizing many other phosphorus compounds at trace levels.

This simple and rapid method for DMMP identification and analysis can be applied to aqueous solutions using ESI, and it then shows a detection limit in the low parts per billion range. The method therefore combines high specificity with high sensitivity, and it is expected to be applicable to the selective detection of chemical warfare agents such as sarin in air and in water since sarin gives a suitable phosphonium ion, $CH_3P(O)F^+$, of *m*/*z* 81 in its electron ionization mass spectrum.[238] The result with the simulant DMMP demonstrates the capability of the Eberlin reaction in highly selective trace organic analysis.

5.3.2. Explosives

Fragmentation of analyte ions followed by ion/molecule reactions of the resulting fragment ions represents a general strategy for identifying classes of compounds with high selectivity.[103] Besides the example of phosphonium ions shown in Scheme 31, another good example is the application of the Eberlin reaction to identification of the explosive TNT (2,4,6-trinitrotoluene). The vinylated TNT ion $[TNT + C_2H_3]^+$ of *m*/*z* 254 easily fragments upon CID to yield an arylnitrenium ion, which undergoes the Eberlin reaction with dioxolanes.[152] Thus, $[TNT + C_2H_3]^+$ of *m*/*z* 254 itself was selected and collided with the Eberlin reagent of 2,2-dimethyl-1,3-dioxolane. As displayed in Figure 20, both the fragment ion, 4-methyl-3,5-dinitrophenylnitrenium of *m*/*z* 196, and its Eberlin reaction product ion of *m*/*z* 240 are formed. The formation of two characteristic products of *m*/*z* 196 and 240 facilitates the allocation of this characteristic ion/molecule reaction and allows selective detection of TNT in mixtures using mass spectrometry. The selectivity stems from both the unique fragmentation behavior and the diagnostic products of the ion/molecule reaction.

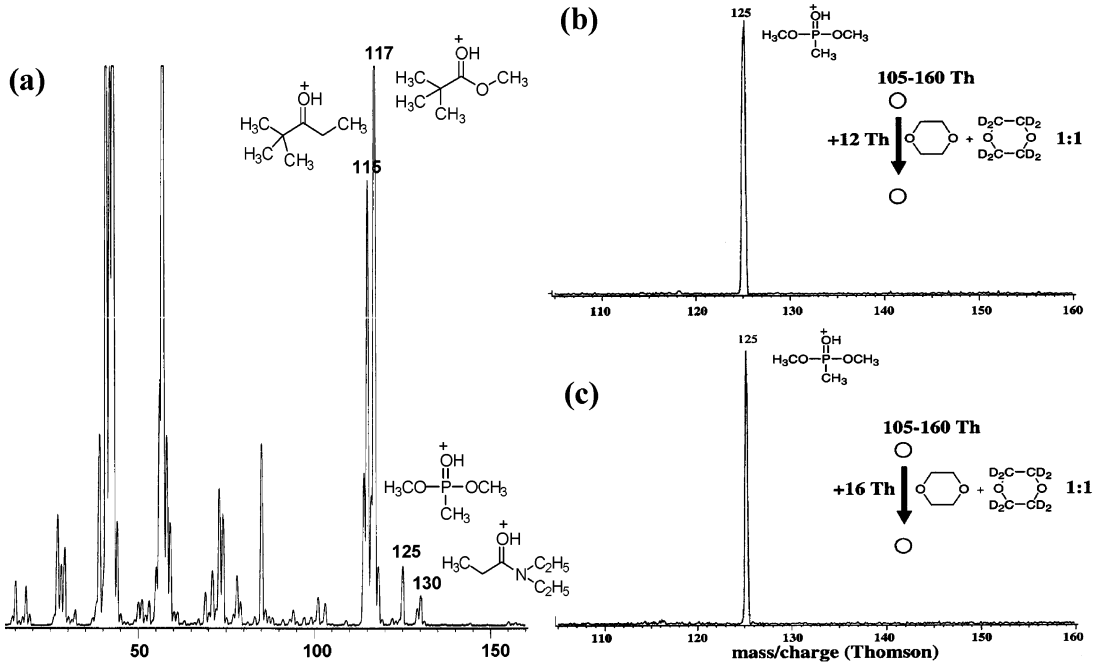


Figure 19. Constant neutral gain mass spectra after isobutane chemical ionization of a mixture of 2,2-dimethyl-3-pentanone, methyl trimethyl acetate, DMMP, and *N*,*N*-diethyl propionamide (CI spectrum is shown in panel a). 1,4-Dioxane and 1,4-dioxane-d_8 (1:1 by volume) is used as the neutral collision gas, and Q1 is scanned from *m*/*z* 105 to *m*/*z* 160, while Q3 scans the corresponding product ions with a mass/charge offset of 12 Th (*m*/*z* units) in panel b and 16 units in panel c. Reprinted with permission from ref 218. Copyright 2003 Elsevier.

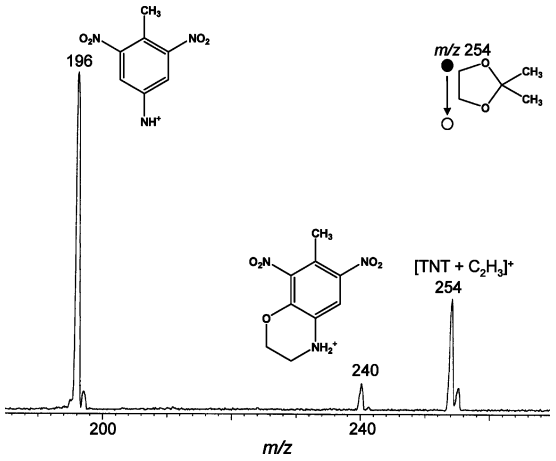


Figure 20. Double-stage MS^2 mass spectrum showing products of the ion/molecule reaction of the vinylated TNT $[TNT + C_2H_3]^+$ of *m*/*z* 254 with 2,2-dimethyl-1,3-dioxolane. Reprinted with permission from ref 152. Copyright 2004 Elsevier.

Because the nitronium ion NO_2^+ is a natural diagnostic ion for many explosives such as TNT, royal demolition explosive (RDX), and pentaerythritol tetranitrate (PETN), Eberlin reactions of NO_2^+ can potentially be applied for broad-range selective screening of this group of target compounds.[153] With 2,2-dimethyl-1,3-dioxolane, the gaseous NO_2^+ ion reacts efficiently by transacetalization to form a characteristic and unique product ion of *m*/*z* 90 (Scheme 19). Enhanced selectivity can be achieved by dissociating the ion of *m*/*z* 90, which upon CID forms mainly NO^+ of *m*/*z* 30. Detection of the diagnostic NO_2^+ ion has then be proposed to be performed using EI in miniaturized ion traps.[239] Owing to minimal pumping requirements, EI has been easily implemented in most miniaturized equipment for on-site field inspection. With use of ion trapping devices, ions of *m*/*z* 46 could be trapped for relatively long times for highest sensitivity. Also in ion traps, the double-reaction monitoring approach, *m*/*z* 46 → *m*/*z* 90 → *m*/*z* 30, could be easily implemented for highly selective broad-range MS screening of organic nitrate explosives.

5.4. Atmospheric Pressure Eberlin Reactions

Gas-phase ion chemistry under high-pressure conditions is a subject of growing interest[88,240−242] for two reasons: (i) all chemical species encountered along the reaction coordinate are thermally equilibrated with the buffer gas, which allows the observed rate constants of ion/molecule reactions to be interpreted rigorously in terms of candidate mechanisms and potential energy surfaces for that reaction;[240,243] (ii) the structural and stereochemical information derived from gas-phase ion chemistry under high pressure conditions, including atmospheric pressure, should be more fully comparable with data from solution chemistry than low-pressure data, thus allowing meaningful correlations between gas-phase and condensed-phase ionic reactivity.[242] An early example of an ion/molecule reaction carried out in an atmospheric pressure capillary inlet reactor based on an ESI interface to a quadrupole mass spectrometer involved the study of proton transfer between amines and multiply protonated proteins by Smith.[124,125] Smith also observed protonated adenosine 5′-monophosphate (AMP) as the product of charge inversion in the reaction of $[AMP-H]^-$ with multiply charged positive macroions using merged gas streams at near atmospheric pressure.[244] Recently, the formation of TNT Meisenheimer

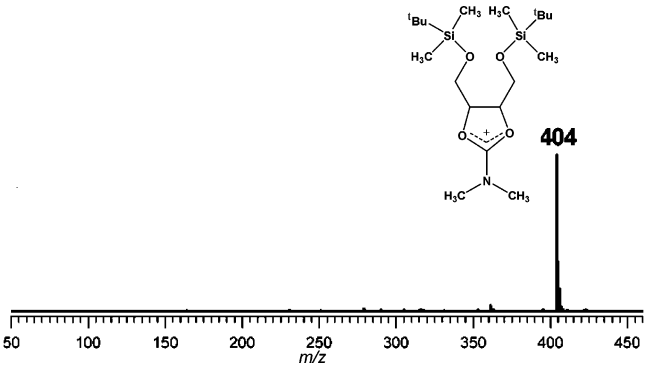
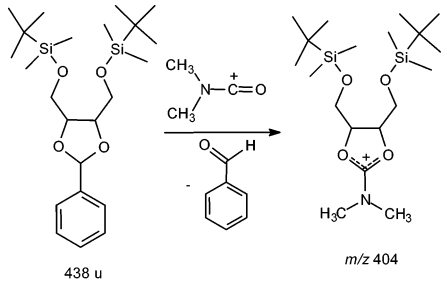


Figure 21. APCI background-subtracted mass spectrum showing products of the atmospheric pressure Eberlin reaction of the acylium ion $(CH_3)_2N-C^+=O$ of *m*/*z* 72 with the cyclic acetal **e**. A similar spectrum was observed under analogous ESI conditions. Reprinted with permission from ref 158. Copyright 2003 American Chemical Society.

complex[245] and the interaction between piperidine and multiply charged lysozyme ions generated by electro-sonic spray ionization (ESSI)[246] under atmospheric pressure has been reported. Eberlin reactions of acylium ions have also been observed to occur under atmospheric pressure under in-source ion/molecule reaction conditions.[158]

In the experiment, tetramethylurea (TMU) was added into an acetal solution as a dopant and then injected into the ESI or APCI source. The basic TMU dopant is protonated preferentially during APCI or ESI; the labile protonated TMU then undergoes dissociation to give $(CH_3)_2N-C^+=O$, the least acidic and the most reactive acylium ion so far tested. To form the acylium ion with the highest yield, its residence time within the ion source region was increased and low-energy collisions were favored with the neutral acetal by using a small potential bias applied to the cone and extractor (e.g., 1 and 40 V, respectively). As an example, Figure 21 displays clearly the product MS spectrum showing the reaction of $(CH_3)_2N-C^+=O$ with acetal **e** (Scheme 32) under

Scheme 32

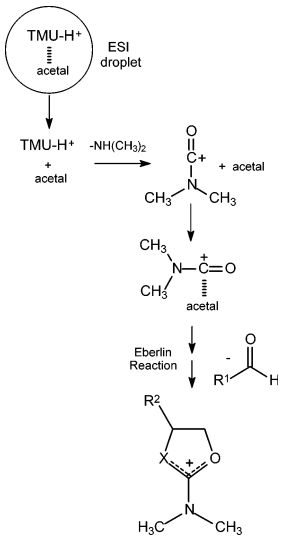


e

such *in-source* ion/molecule reaction conditions.

Atmospheric-pressure ion/molecule reactions, performed under in-source ion/molecule reaction conditions for ESI or APCI, have expanded the range of the Eberlin reaction to acetals of higher mass, polarity, and structural complexity, as illustrated in Scheme 32. Polar transacetalization, previously limited to more volatile and lighter neutrals and introduced into the gas phase by volatilization or by ultrafast heating, is now applicable to considerably more polar and heavier molecules. A feature of the Eberlin reaction performed under atmospheric pressure ion/molecule conditions is that proton transfer and hydride abstraction have been observed to occur to much smaller extents than seen under vacuum.

Scheme 33



Mechanisms for ESI (Scheme 33) and APCI in-source Eberlin reactions have been rationalized using, for ESI, for instance, the ion evaporation model.[158] Both protonated TMU and the neutral acetal evaporate simultaneously from the ESI droplet into the gas phase; then gaseous highly labile protonated TMU dissociates readily by dimethylamine loss to form the reactant acylium ion because of the weak amide bond in the protonated urea molecule. When the acylium ion−acetal complex is formed, irreversible polar transacetalization occurs within this gaseous ion−molecule complex yielding the observed cyclic ionic acetal product.

6. Conclusions

This review highlights the large body of work published on the Eberlin acetalization and transacetalization reactions and related gas phase ion/molecule reactions. The reaction has been found to occur for many classes of amphoteric cations with dual Lewis acidity and basicity with cyclic acetals, diols, and related compounds. Extensive fundamental, synthetic, and analytical applications of the gas-phase Eberlin reaction, as well as close connections with condensed-phase chemistry (functional group protection and solvated ionic reaction), have been reviewed. The Eberlin reaction is versatile in that it (i) provides deprotecting/protecting chemistry in the gas phase for which it is the cationic variant of the acetalization/transacetalization reaction of neutral carbonyl compounds, (ii) suggests new reagents for application in solution, such as new deprotecting reagents for acetals, (iii) functions analogously to the corresponding condensed phase acetalization or transacetalization reactions of aldehydes and ketones with acetals or diols, as structurally diagnostic and class-selective reactions for both reactant ions and neutrals revealing specific functional groups, substituent positions and ring sizes, (iv) discriminates between structural isomers and diastereomers and provides assignments of positional isomers by mass spectrometry, (v) offers concise routes to the gas-phase synthesis of various heterocyclic compounds, (vi) allows selective detection of such target compounds as chemical warfare agents and explosives, and (vii) not only occurs efficiently in the low-pressure mass spectrometric gas-phase environment but can also be performed at atmospheric pressure via electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI), as well as in solution, thus offering the potential of more meaningful correlations between gas-phase and condensed-phase ion chemistry than hitherto possible. Eberlin reactions have also been observed under ambient conditions using desorption electrospray ionization (DESI),[248] and this convenient method expands the scope of the reaction.

Further study of this versatile reaction appears to be promising for several reasons: (i) the Eberlin reactivity of other amphoteric species including nonmetal ions (e.g., phosphenium ions $(RO)_2P^+$) or heavy-metal-centered ions (e.g., Cd and Fe ions with a five- or six-membered ring consisting of a Cd/Fe center and two coordinated oxygen atoms),[247] (ii) the emergence of new ionization methods such as ESI and APCI and of more powerful mass analyzers, which together will allow the study of a wider range of interactions between amphoteric ions and heavier and more polar neutral reagents, (iii) the ability of the Eberlin reaction to be systematically studied under atmospheric pressure, either in the gas phase, at the gas phase/solution interface, at surfaces, or in bulk solution (such studies should elucidate the roles of solvent, pressure, and temperature on the reaction and help extend the field of ion chemistry beyond its conventional boundary of the gas phase), (iv) the fact that the ionic heterocyclic product synthesized in an Eberlin reaction could be mass-selected and soft-landed on a surface[249] meaning that such a method of product collection should also be suitable for other types of ion/molecule reactions, and (v) the potential biological applications of the Eberlin reaction remains to be investigated, prompted by the fact that peptides and proteins contain many carbonyl functional groups and carbohydrates have acetal moieties, which are potential Eberlin reactive sites.

7. Acknowledgments

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