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Review

Gas-phase polar cycloadditions

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Abstract

The dilute gas-phase environment of mass spectrometers provides versatile and convenient medium in which chemists can form a great variety of ionic species and study their intrinsic reactivity exploring reaction mechanisms and screening for new reactions and their applications. Recent and illustrative examples of gas-phase polar cycloadditions of even and odd-electrons ions, which have been observed (some for the first time) in the solvent- and counter ion-free environment of mass spectrometers, are presented. Synthetic and analytical applications of such reactions and correlations with analogous reactions observed in solution are also discussed.

Keywords: Cycloaddition reactions; Pericyclic reactions; Mass spectrometry; Structure selective gas-phase ion/molecule reactions; Reaction mechanisms

1. Introduction

The ability to form a diverse and multiform set of cyclic structures is one of the most outstanding features of organic molecules. Nature and the synthetic chemist use therefore a great variety of cyclization reactions to form marvelous cyclic molecules of many types and shapes, and important functions. In cycloaddition reactions [1], two or more unsaturated molecules (or parts of the same molecule) combine to form a cyclic product with net reduction of bond multiplicity, and the most famous example of such reactions is that discovered in 1928 by Diels and Alder [2]—the [4 + 2] Diels–Alder cycloaddition.

Cycloadditions may be *concerted* (*pericyclic*) or *stepwise*. Concerted cycloadditions proceed via a single transition state with no intermediates, and bond making and bond breaking both contribute to the structure at the transition state. Stepwise cycloadditions proceed via two discrete bond-making steps, that is, via an addition plus cyclization mechanism, although stereospecificity may still be observed when the bond-making cyclization step occurs faster than rotation about bonds in the addition intermediate. Even in concerted cycloadditions, the extent of bond making at the two sites may be different at the transition state.

The symbolism $[i + j + \ldots]$ for a cycloaddition identifies the numbers $i + j + \ldots$ of electrons in the interacting units that participate in the transformation of reactants to products. The symbol a or s (a: antarafacial, s: suprafacial) is sometimes added to designate the stereochemistry of addition to each fragment, and a subscript specifying the orbitals: σ, π, or n. Thus (a) the Diels–Alder reaction is a $[\pi 4_s + \pi 2_s]$ cycloaddition whereas (b) is a $[\pi 14_a + \pi 2_a]$ cycloaddition (Scheme 1) [3].

Although neutral reactants are normally employed, many cycloadditions start with, or involve cations or anions as their key reactants, and are therefore termed as *polar cycloadditions* [4]. Ionized molecules are also sometimes advantageously used in *charge-promoted* or *charge-catalyzed* (“electron-hole” catalyzed according to Bauld et al. [5]) radical cation cycloadditions particularly for unactivated alkynes and alkenes. For polar cycloaddtions, one should denote that a charged reactant is used. Therefore, using polar Diels–Alder cycloadditions of radical cations as an example, either the $[3^+ + 2]$ or $[4 + 1^+]$ symbolism denotes that an ionized diene (3^+) or ionized dienophile (1^+) with odd number of electrons participates. For polar Diels–Alder cycloadditions of even-electron cations, either the $[4^+ + 2]$ or $[4 + 2^+]$ symbolisms are used to describe the reaction [4].

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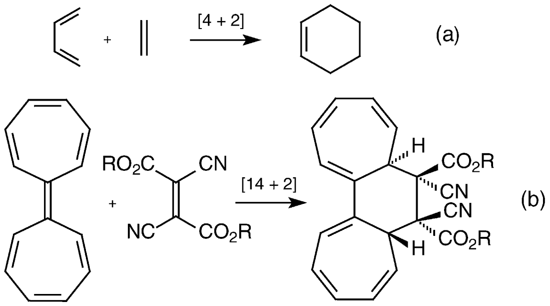


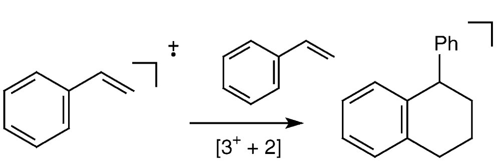
Scheme 1.

In the dilute gas-phase environment, polar cycloadditions of solvent- and counter ion-free ions have been studied using a variety of mass spectrometric (MS) techniques [6]. These MS studies have revealed new reactions and shed light to intrinsic reactivities and reaction mechanisms. Important analytical and synthetic uses for these often so selective ion/molecule reactions have also been found. Because of high selectivity, for molecular class (dienes and dienophiles for instance) and geometry (*s-cis* conformation for a concerted Diels–Alder cycloaddition), cycloadditions are prime candidates for class-selective and structure diagnostic reactions. Therefore, analytical applications of these reactions are promising and have been already demonstrated, but there is still much to be explored.

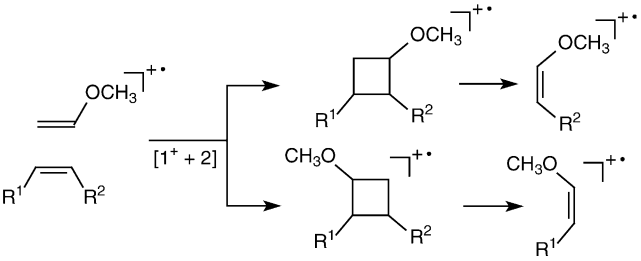
Whether gas-phase polar cycloadditions occur in a concerted or stepwise fashion has been difficult to determine (for a controversial case see [7]), hence most often either concerted or stepwise pathways are assumed. Also, the energy released upon exothermic gas-phase ion/molecule reactions are deposited on products, hence nascent ionic cycloadducts may either isomerize or dissociate, or both. This peculiarity of polar cycloadditions performed in the gas phase sometimes precludes the observation of the intact cycloadduct. It has also been challenging to prove that indeed cyclic adducts are formed, or which regioisomer dominates, and sometimes formation of cyclic products or a specific regioisomer have simply been assumed, and incorrect structural assignments are therefore possible. Often, however, theoretical calculations have been used to show that cyclic products should dominate since they are found to be, intrinsically, far more stable than acyclic alternative products. Isotopic labeling and "authentic" reference ions have also been used in a number of cases as experimental proofs for the structural assignments of cyclic adducts or regioisomers.

2. Gas-phase radical cation cycloadditions

Early MS studies on gas-phase cycloadditions often tried to draw correlations between gas-phase and solution reactions, and investigated mainly radical cation cycloadditions, such as the pioneering report by Wilkins and Gross [8] on the cyclodimerization of ionized styrene (Scheme 2). These early studies have been thoroughly reviewed by Dass (1990), Kuck and Mormann (2000) and Gronert (2001) [6].

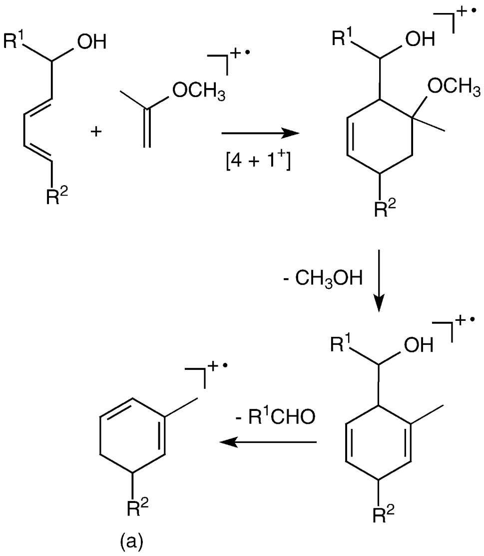


Scheme 2.

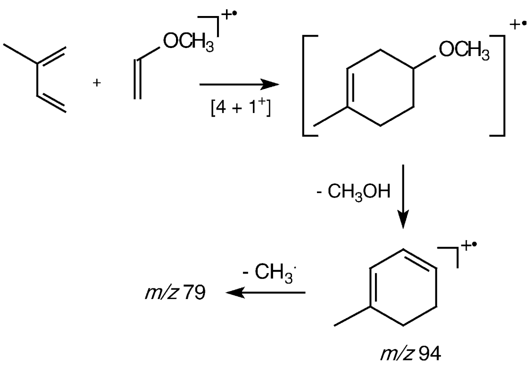


Scheme 3.

Jennings and co-workers [9] performed one of those early gas-phase cycloadditons, that of ionized methyl vinyl ether with olefins and dienes. This reaction has found an interesting analytical application: mono- and di-unsaturated compounds form structurally diagnostic product ions, which are indicative of the location of the initial double bond (Scheme 3) [10]. A typical application for this reaction is that reported by Tabet and co-workers [11] for α-hydroxy conjugated dienes, such as coriolic and dimorphecolic acids and their methyl esters used as self-defensive compounds by plants. After [4 + 1$^+$] cycloaddition and two consecutive neutral losses, a diagnostic fragment ion (a in Scheme 4) is formed, and serves to characterize and locate the unsaturated system of α-hydroxy conjugated dienes.



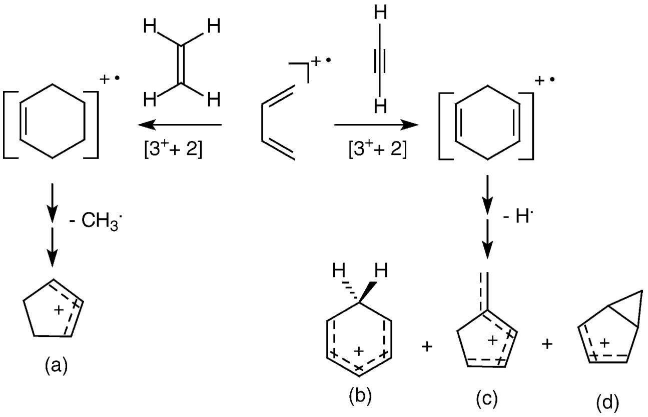
Scheme 4.



Scheme 5.

Isoprene, a major constituent of the biogenic volatile organic compounds (BVOCs) emitted into the atmosphere, plays a significant role in the undesirable formation of tropospheric ozone. However, fast and reliable determination of atmospheric isoprene has been challenging. To accomplish such a task, Shepson and co-workers [12] proposed a fast, sensitive, and selective method that takes advantage of the tendency of isoprene, a conjugated diene, to react by cycloaddition. Gas-phase polar $[4 + 1^+]$ cycloaddition of isoprene with ionized methyl vinyl ether was found to occur readily, and the nascent cycloadduct to dissociate promptly by ethanol loss to yield the diagnostic ion of *m/z* 94 (Scheme 5). Further selectivity can also be gained by sequential reaction monitoring (isoprene → *m/z* 94 → *m/z* 79) since upon collision-induced dissociation (CID), the mass-selected fragment ion of *m/z* 94 loses a methyl radical.

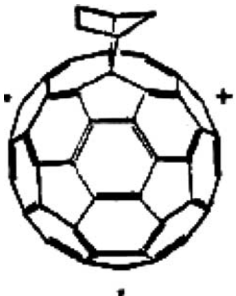
By simply removing one electron from one reaction partner, radical cation-initiated cycloadditions [5] promotes the addition between poorly-reactive or "non-reactive" neutrals, and their reaction rates are several orders of magnitude greater than those of the corresponding neutral reactions. These reactions are therefore important and versatile tools for the synthetic chemist, but their mechanisms are still poorly documented. Bouchoux et al. [13] studied therefore, both experimentally and theoretically, the prototypical Diels–Alder cycloaddition reactions of ionized 1,3-butadiene with neutral acetylene and ethylene, and performed a detailed analysis of the structures of reaction products (Scheme 6). Reaction with ethylene gives the cyclopentenyl cation (a) as the major product. For reaction with acetylene, the nascent cycloadduct (ionized 1,4-cyclohexadiene) was found to undergo either H atom loss to form the benzenium ion b (∼55%), or hydrogen-atom migrations and ring-contraction processes to form the two most stable protonated forms of fulvene, that is: α-protonated fulvene c (∼25%) and the bicyclo[3.1.0]-hexenyl cation d (∼20%). A mechanism, supported by ab initio calculations, was proposed to account for this product distribution.



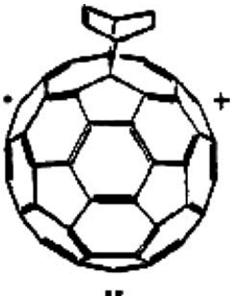
Scheme 6.

Grützmacher and Barkow [14] also found that the much greater polar cycloaddition proclivity toward norbornadiene (Scheme 7), as compared with the isomeric ionized molecules of benzocyclobutene and styrene, is highly diagnostic for ionized *ortho*-quinodimethene. Polar $[3^+ + 2]$ cycloaddition is followed by cycloreversion of the gaseous Diels–Alder adduct to give both neutral cyclopentadiene and ionized 1,4-dihydronaphthalene (1,4-dialin), which dissociates further by H and H_2 loss (ionized naphthalene is therefore likely formed).

Bohme and co-workers [15] reacted the gaseous ionized fullerenes $C_{60}^{\bullet+}$ and $C_{70}^{\bullet+}$ with a variety of cycloalkenes and acyclic and cyclic dienes, and found that $C_{60}^{\bullet+}$ displays remarkable selectivity toward two cyclic dienes: 1,3-cyclopentadiene and 1,3-cyclohexadine. The reaction was proposed to occur by $[4 + 1^+]$ cycloaddition of $C_{60}^{\bullet+}$ that forms cycloadducts I and II (below). $C_{70}^{\bullet+}$ also undergoes cycloaddition with 1,3-cyclopentadiene and 1,3-cyclohexadine but five to six times slower than $C_{60}^{\bullet+}$. The intrinsic reactivity ratio of $C_{60}^{\bullet+}$ and $C_{70}^{\bullet+}$ measured in the gas phase for cycloaddition with 1,3-cyclopentadiene was found to be near the same as that measured in solution.

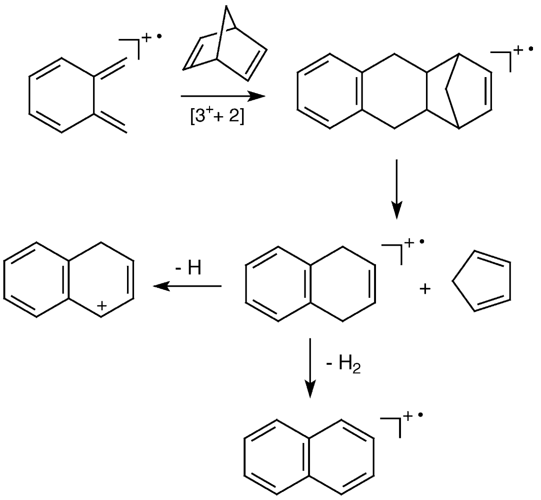


I



II

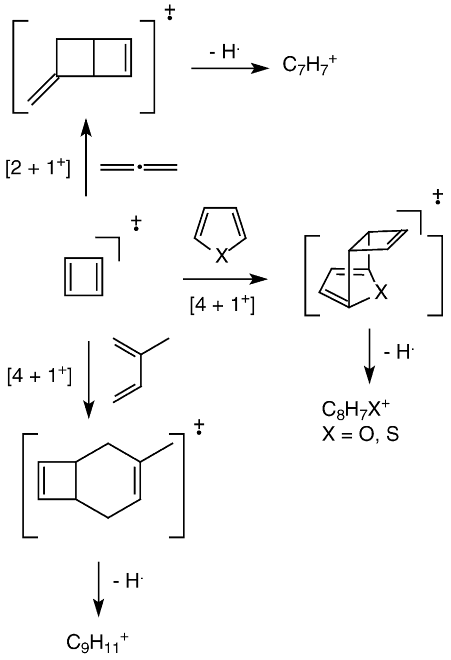
The ease by which gaseous $C_4H_4^{\bullet+}$ isomers interconvert make this ionic system a challenging case for differentiation by mass spectrometry. Structural characterization by CID has proven particularly difficult because the energy deposited to produce dissociation often causes unintended isomerizations. Cooks and co-workers [16] found, however, that the non-aromatic ionized cyclobutadiene can be easily distinguished from other $C_4H_4^{\bullet+}$ isomers (ionized



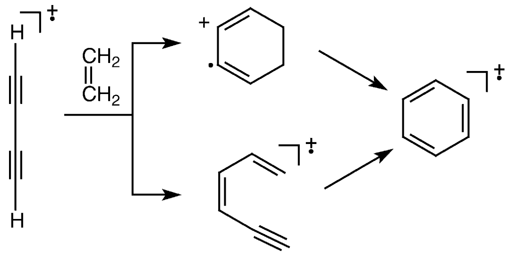
Scheme 7.

vinylacetylene, butatriene, and methylene cyclopropene) because it displays much greater impetus toward gas-phase cycloadditions with allene, isoprene, furan and thiophene (Scheme 8).

Wenthold and co-workers [17] have recently shown that the ionized form of the UV molecular shield of the Saturn's moon Titan, diacetylene, undergoes polar cycloaddition with ethylene to yield ionized benzene. A selective ion/molecule reaction and energy-resolved MS experiments have demonstrated that ionized benzene is formed, but the reaction mechanism could not be so well established. Two routes (not fully depicted) for this interesting cycloaddition reaction were proposed (Scheme 9).



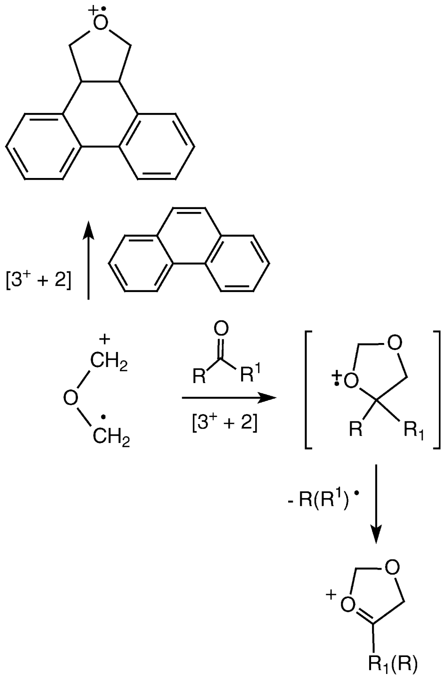
Scheme 8.



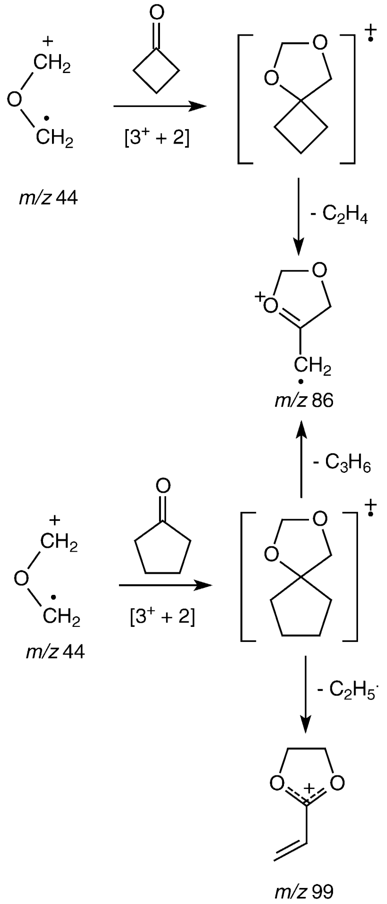
Scheme 9.

2.1. Distonic ions [18]

Ions with *formal* [19] separation of charge and spin, and some with high degree of *actual* charge-spin separation [20], are known as distonic ions. Among these interesting bidentate species, those arising formally from the ionization of ylides (α-distonic ions) are potential candidates for *1,3-polar* cycloadditions. Examples of such reactions for distonic ions are, however, rare. We [21] observed the first gas-phase 1,3-polar cycloaddition of an ionized ylide when performing ion/molecule reactions of the mass-selected α-distonic ion $^{+}CH_2OCH_2^{\bullet}$ (the ionized form of the prototypical ionized carbonyl ylide) with carbonyl compounds. The reaction occurs across the C=O bond yielding ionized 4,4-dialkyl-1,3-dioxolanes as the nascent cycloadducts, which rapidly dissociates to cyclic 4-alkyl-1,3-dioxolanylium ions (Scheme 10). In reactions of $^{+}CH_2OCH_2^{\bullet}$ with cyclobutanone, for instance, the nascent cycloadduct dissociates promptly by ethylene loss to form an abundant product ion of *m*/*z* 86 (Scheme 11 and Fig. 1a). In reactions of $^{+}CH_2OCH_2^{\bullet}$ with cyclopentanone, the nascent cycloadduct dissociates by both $C_2H_5^{\bullet}$ and

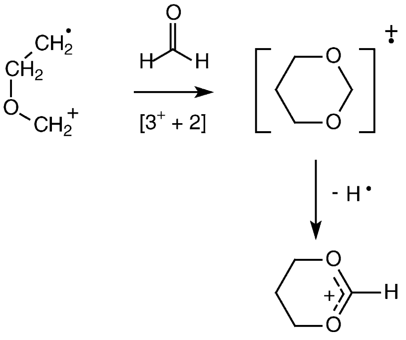


Scheme 10.

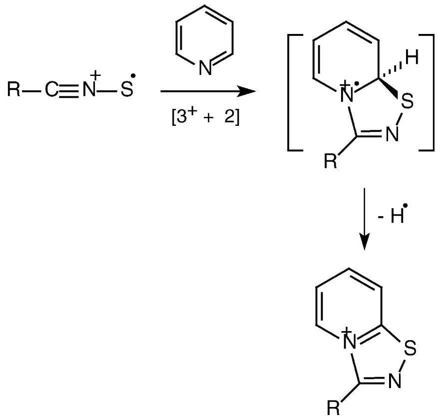


Scheme 11.

C_3H_6 loss (Scheme 11). Experimental evidence for cyclic products has been collected by comparing CID product ion mass spectra to those of isomeric and reference ions. Theoretically, the preferential formation of cycloaddition products has been corroborated by ab initio calculations.



Scheme 12.



Scheme 13.

Cycloaddition with $^{+}CH_2OCH_2^{\bullet}$ has also been incidentally suggested by Lange [22] as the source of a unique $[M + 44]^{+\bullet}$ product in the oxirane CI mass spectrum of phenanthrene (Scheme 10), a common dienophile with an activated C(9)–C(10) double bond. Hammerum et al. [23] also found that the homologous β-distonic ion $^{+}CH_2OCH_2CH_2^{\bullet}$ undergoes regiospecific cycloaddition with formaldehyde followed by fast dissociation of the nascent cycloadduct (ionized 1,3-dioxane) by H loss (Scheme 12). The reaction course has been followed by deuterium labeling and the authenticity of the cyclic product probed via comparison of its CID chemistry with that of a reference ion, that is, the $[M - H]^{+}$ fragment ion from ionized 1,3-dioxolane.

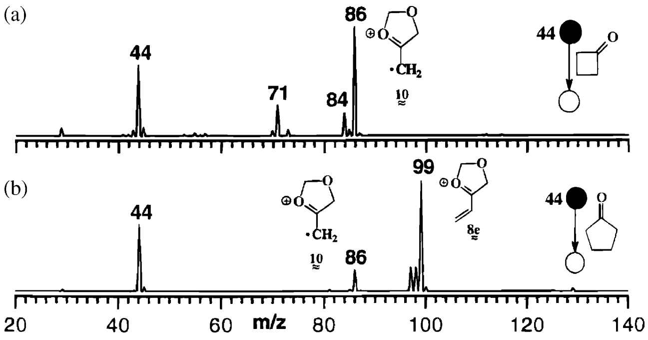


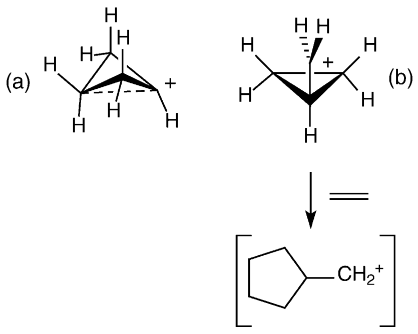
Fig. 1. Product ion (MS^2) mass spectra for the reactions of the mass-selected distonic ion $^{+}CH_2–O–CH_2^{\bullet}$ of m/z 44 with (a) cyclobutanone and (b) cyclopentanone. Note the major cycloaddition product ions of m/z 86 (marked as 10) in (a) and m/z 99 (marked as 8e) and 86 (10) in (b). For mechanistic details see Scheme 11. $CH_2^{+\bullet}$ transfer also occurs yielding the ions of (a) m/z 84 and (b) m/z 98 as minor products. Reproduced with permission for reference [21].

Ionized nitrile sulfides, another class of ionized ylides (α-distonic ions) were reported by Flammang and co-workers [24] to undergo an interesting $[3^{+} + 2]$ cycloaddition with pyridine followed by rapid H atom loss. This 1,3-polar cycloaddition allows gas-phase synthesis of aromatic thiazolopyridinium ions (Scheme 13).

3. Polar cycloadditons with even-electron cations

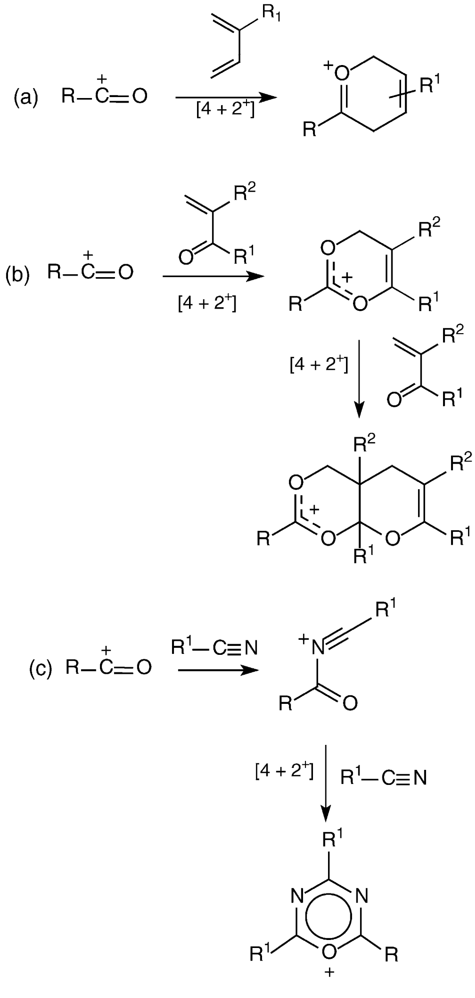
3.1. Carbocations

Cyclopropylcarbinyl and cyclobutyl substrates solvolyze at unexpectedly high rates to carbocations, presumably generating either directly or indirectly the symmetrically stabilized cyclopropylcarbinyl cation b (Scheme 14) [25].



Scheme 14.

Therefore, the structures and isomerizations of $C_4H_7^+$ cations have attracted much interest. Gross and co-workers [26] used a structure selective polar cycloaddition reaction with ethene to characterize and distinguish the gaseous cyclopropylcarbinyl cation (b, Scheme 14) from the isomeric bycyclobutonium ion (a), the prototypical “non-classical” carbocation. The reaction for the cyclopropylcarbinyl cation was proposed to form, by an interesting ring expansion process, the nascent cyclopentylcarbinyl cation, a primary carbocation that likely undergoes further isomerization (Scheme 14).



Scheme 15.

3.2. Acylium and thioacylium ions

In the dilute gas-phase environment of mass spectrometers, acylium and thioacylium ions are long-lived and very common, and they display a rich gas-phase chemistry which includes cyclization and cycloaddition reactions (Scheme 15) [27]. Cooks and us have found that gaseous acylium ions (and sometimes also thioacylium ions) undergo (a) polar $[4 + 2^+]$ cycloaddition with dienes [28] and (b) mono (and double) polar $[4 + 2^+]$ cycloaddition with heterodienes [29]. In (c) double nitrile [30] addition to acylium ions, the second reaction step can also be viewed as a polar $[4^+ + 2]$ cycloaddition.

Cooks and co-workers [31] have also found that its structure selective cycloaddition reactivity differentiates the acetyl cation from other $C_2H_3O^+$ isomers, and then applied the interesting three-dimensional MS^3 familial spectrum [32] of Fig. 2 to investigate, via this selective polar cycloaddition reaction, the structure of $C_2H_3O^+$ product ions of *m/z* 43 arising from CID of mass-selected 3-octanone EI-parent ions. In Fig. 2, the angled axis displays the CID parents of *m/z* 43 ions whereas the horizontal axis displays the product ions arising from ion/molecule reactions with isoprene. The acetyl cation is characterized by a 10:1 abundance ratio for the product ions of *m/z* 111 and 81, as is so for the ion of

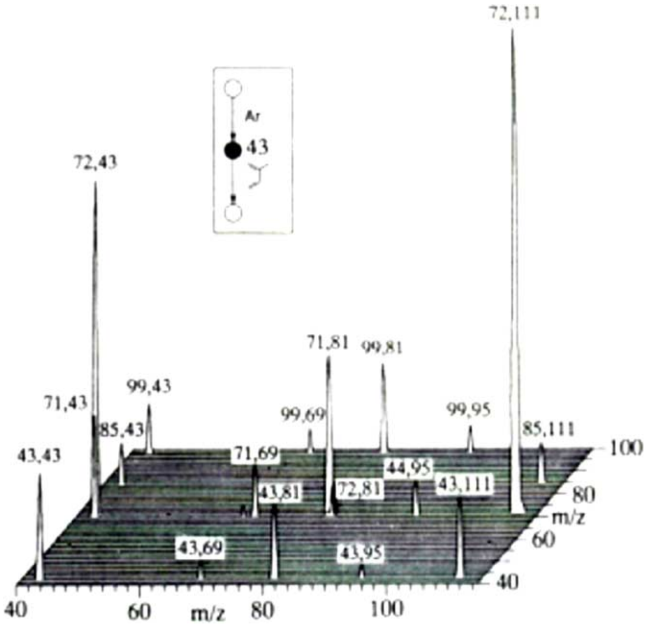
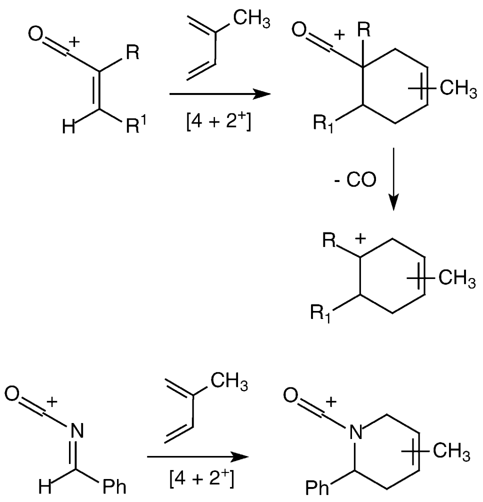


Fig. 2. Three-dimensional MS^3 familial spectrum for major 70 eV EI ions of 3-octanone acquired by selecting ions of *m/z* 43 as the intermediate. The angled axis displays the parents of *m/z* 43 ions while the horizontal axis displays the product ions arising from these CID-generated *m/z* 43 ions upon ion/molecule reactions with isoprene. Mass assignments refer to the initial and final product ions. Reproduced with permission from reference [31].



Scheme 16.

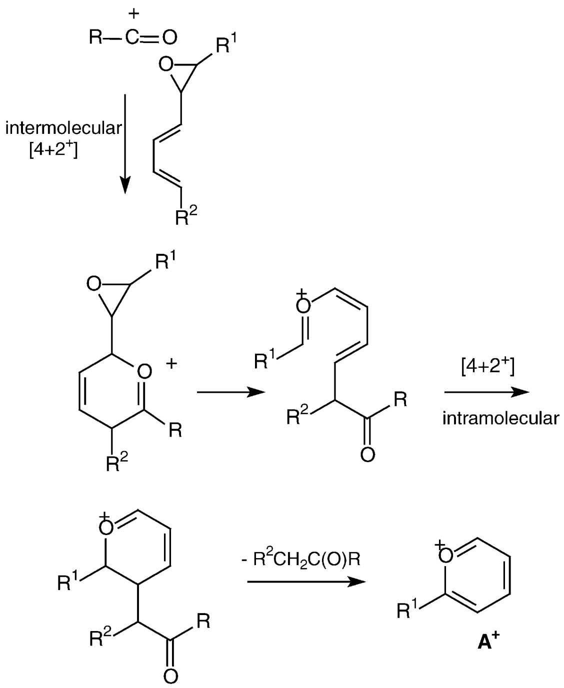
m/z 43 arising from CID of the precursor ion of m/z 72 (74,43 in Fig. 2). Note the nearly 10: 1 abundance ratio for the peaks assigned as 72,111 and 72,81. In contrast, the ionic population of m/z 43 which arise from CID of the m/z 99 ion (99,43) is not composed of acetyl cations since it fails to react with isoprene to form the cycloadduct of m/z 111 yielding instead mainly the product ion of m/z 81. These reactivity trends agree with the expected structures of the precursor ions, that is: $n\text{-}C_5H_{11}CO^+$ for m/z 95 and $C_2H_5COCH_3{}^{+\bullet}$ for m/z 72.

Cycloadditions with the acetyl cation is also likely the structure selective reaction responsible for abundant $[M + 43]^+$ adducts in oxirane CI (a plasma which contains nearly 28% of the acetyl cation) of dienes. For instance, the $[M + 43]^+$ ion constitutes the major product and is therefore detected as the base peak in the oxirane CI mass spectrum of pentacosa-7,9-diene [22].

Cooks and us [28] also observed an interesting "charge-remote"-type of cycloaddition, that is, α,β-unsaturated acylium ions have been shown to undergo regioselective polar cycloaddition across the α,β-double bond (Scheme 16).

Sharifi and Einhorn [33] then applied polar $[4 + 2^+]$ cycloaddition of acylium ions to differentiate six isomeric C15 conjugated diene epoxides. The cycloadducts do not dissociate by retrocycloaddition (RDA, a common feature of such adducts) [27] but dissociation occurs by pathways favored by the side epoxide ring leading mainly to stable, aromatic pyrilium ions. These ions display m/z ratios that correlate clearly with either the epoxide or diene substituents thus serving as structurally diagnostic ions for isomer differentiation. Scheme 17 shows the proposed reaction/dissociation pathway to a typical diagnostic ion: A^+.

Cooks and us, and co-workers, have also reported a number of gas-phase polar $[4 + 2^+]$ cycloadditions with dienes for nitrilium ($RC{\equiv}N^+{-}R$) and immonium ($RRC{=}N^+RR$) ions [34], sulfonium ($RRC{=}S^+{-}R$) [35], the phenyl sulfinyl cation ($PhS^+{=}O$) [36], and gaseous protonated and methy-



Scheme 17.

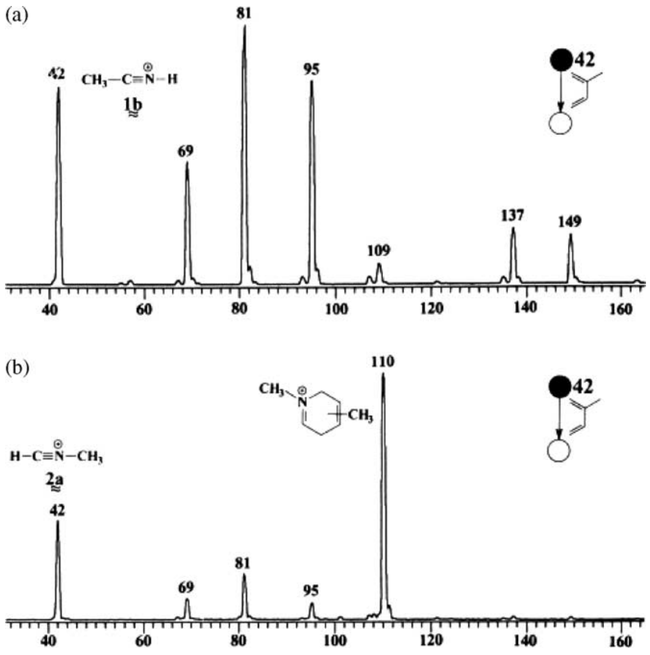
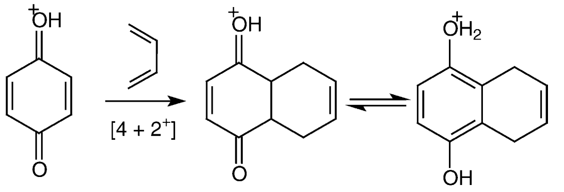


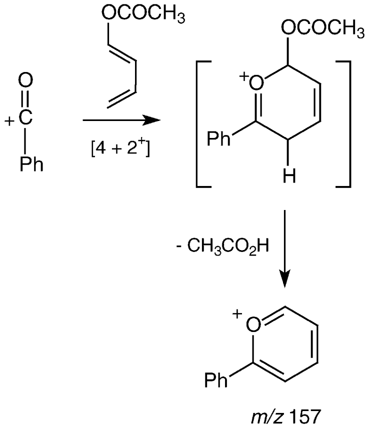
Fig. 3. Product ion (MS^2) mass spectra for the reactions of isomeric ions (a) $CH_3{-}C{\equiv}N^+{-}H$ and (b) $H{-}C{\equiv}N^+{-}CH_3$ of m/z 42 with isoprene. $CH_3{-}C{\equiv}N^+{-}H$ reacts promptly by proton transfer, a reaction that leads to the primary product ion of m/z 69 and a series of secondary product ions, mainly those of m/z 81, 93, 95, 107, 109, 135, and 149. $H{-}C{\equiv}N^+{-}CH_3$ reacts selectively by polar $[4 + 2^+]$ cycloaddition to form mainly the intact cycloadduct of m/z 110. Reproduced with permission from reference [34].



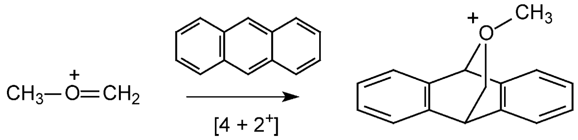
Scheme 18.

lated carbonyl compounds [37]. For nitrilium ions, for instance, the great proclivity of C-protonated methyl isonitrile $\mathrm{H{-}C{\equiv}N^{+}{-}CH_3}$ to undergo cycloaddition with isoprene greatly contrast to the inertness toward such reaction of the isomeric protonated acetonitrile $\mathrm{CH_3{-}C{\equiv}N^{+}{-}H}$ (Fig. 3) [34]. Note that these two isomeric molecules, methyl isonitrile and acetonitrile, display nearly identical EI mass spectra. For protonated ketones, a representative case is that of benzoquinone, a common dienophile in solution Diels–Alder cycloadditions. The protonated molecule of benzoquinone reacts promptly with 1,3-butadiene by polar $[4 + 2^+]$ cycloaddition (Scheme 18), and the tandem mass spectrum for CID of the intact adduct matches that of the authentic ion formed by chemical ionization of the synthetic adduct [37].

We [38] have recently collected compelling evidence for polar $[4 + 2^+]$ cycloaddition of gaseous acylium ions with dienes particularly via reactions with 1-acetoxy-1,3-butadiene (Fig. 4). The nascent cycloadducts were found to dissociate by the loss of an acetic acid molecule to yield stable aromatic pyrylium ions (Scheme 19).



Scheme 19.



Scheme 20.

3.3. Oxonium ions

When using dimethyl ether as a CI gas to screen for organic functional groups, a number of structure selective polar cycloaddition reactions have been observed for an abundant ion in such a CI plasma: the methoxymethyl

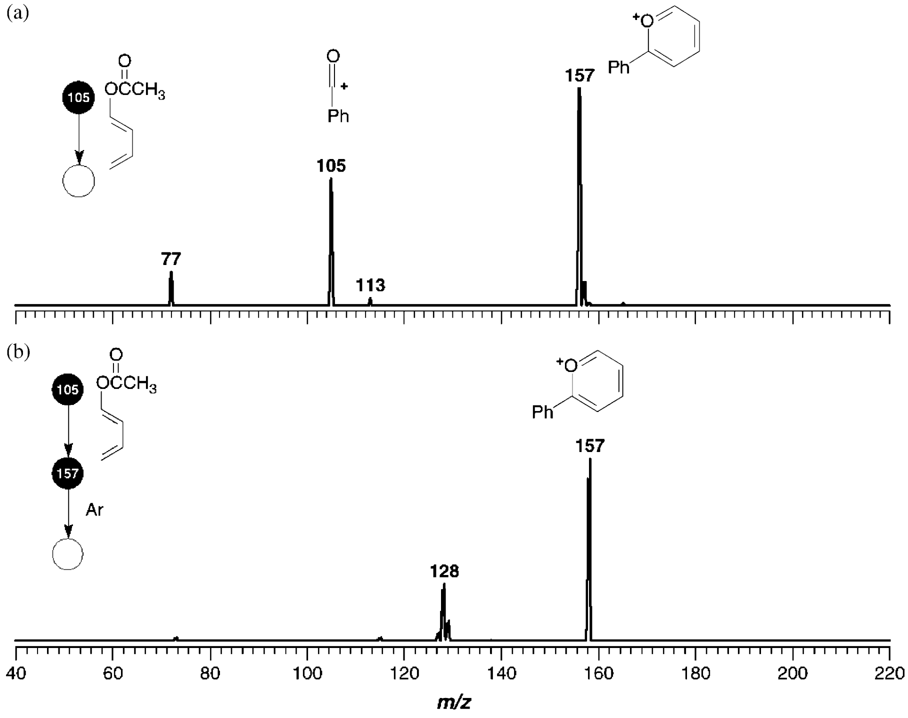
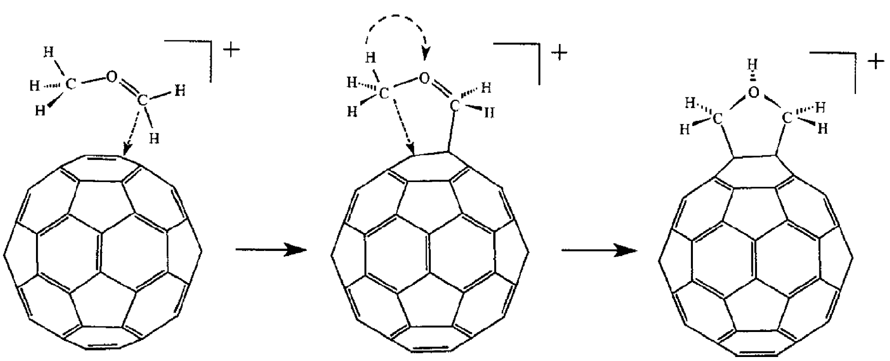


Fig. 4. (a) Product ion (MS^2) mass spectrum for reactions of the acylium ion $\mathrm{Ph{-}C^{+}{\equiv}O}$ of *m/z* 105 with 1-acetoxy-1,3-butadiene (Scheme 19). (b) Sequential product ion mass spectrum for CID of the main reaction product of *m/z* 157. Note in (a) the high yield (ion conversion rate) for the cycloaddition reaction leading nearly exclusively to the ion of *m/z* 157 ascribed as the aromatic 2-phenylpyrylium ion (the ion of *m/z* 77, $\mathrm{Ph^+}$, is a CID fragment of $\mathrm{Ph{-}C^{+}{\equiv}O}$), and in (b) the relative stability of the ion of *m/z* 157 toward CID. Reproduced with permission from reference [38].



Scheme 21.

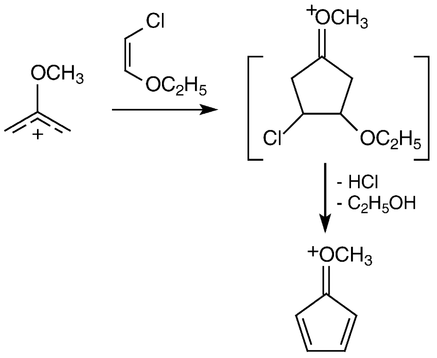
cation $CH_2{=}O^+{-}CH_3$. A number of analytical applications have then been found for some of these reactions, as reviewed recently by Brodbelt [39]. A classical example is that reported by Keough [40] for conjugated dienes and polycyclic aromatic hydrocarbons. Anthracene, for instance, is known to undergo facile Diels–Alder cycloadditions in solution, and was found to exhibit likewise in the gas phase high polar $[4 + 2^+]$ cycloaddition reactivity toward $CH_2{=}O^+{-}CH_3$ (Scheme 20). An abundant adduct of gaseous $CH_2{=}O^+{-}CH_3$ with neutral C_{60} has also been observed by Liu and co-workers [41] in ion/molecule reactions occurring under CI conditions, and theoretical calculations pointed to cycloaddition via the mechanism roughly outlined in Scheme 21.

In one of the earliest (most likely the first) reports on gas-phase polar cycloaddition for even-electron cations, Nibbering and co-workers [42] showed that the 2-methoxyallyl cation adds to enol ethers (EEs) to form methoxycyclopentadienyl cations after 1,2-elimination of neutral molecules from the nascent cycloadduct. Scheme 22 depicts the reaction of this charge-delocalized cation with 1-chloro-2-ethoxyethene.

3.4. Hetarynium ions

The simplest *ortho*-hetarynium ion [43], the mesomeric 2-pyridyl cation, and its *N*-analogue, the 2-pyrimidyl cation, are isoelectronic with *ortho*-benzyne, the simplest and most common aryne. Similarly to *ortho*-benzyne, these cations participate as key and short-lived intermediates in many condensed-phase reactions [44]. In the gas phase, we [45] found that the 2-pyridyl and 2-pyrimidyl cations exhibit a pronounced dienophile character, and that they undergo polar cycloadditions with dienes in reactions that provide "*one-step*" gas-phase synthesis of indolizine and its derivatives (Fig. 5). The term "one-step" has been used to denote that a single annulation reaction was employed to construct the indolizine byciclic ring via formal pyrrole ring fusion. Likely however, the reaction proceeds via a number of consecutive steps (Scheme 23). We [46] then used this selective reactivity for the *ortho* isomers to locate the charge, and therefore the original substituents in a "nearly-absolute" MS-only method for the structural assignment of isomeric pyridine and pyrimidines.

According to the proposed mechanism (Scheme 23), which has been corroborated by ab initio calculations (Fig. 6), polar $[4 + 2^+]$ cycloaddition dominates for the reaction of hetarynium ions with conjugated dienes, and forms cyclic adducts (a) that are by far more stable than the alternative acyclic adducts (b). However, owing to the very high energy content of the nascent cycloadducts (cycloaddition is exothermic by as much as −113.2 kcal/mol for the case study of Fig. 5), ions a ring-contract to ions d: that is, ions a are converted into the even more stable cations d by a ring-opening plus re-cyclization process mediated by ions b and c. To release some of their high energy content (now



Scheme 22.

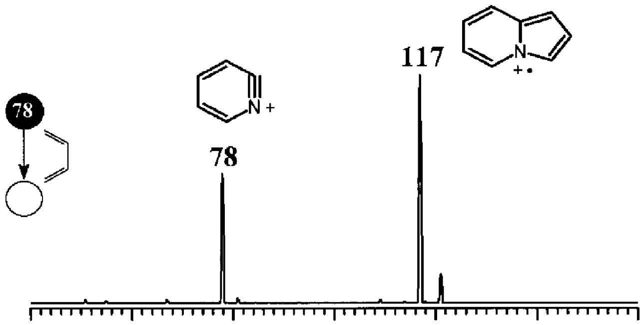
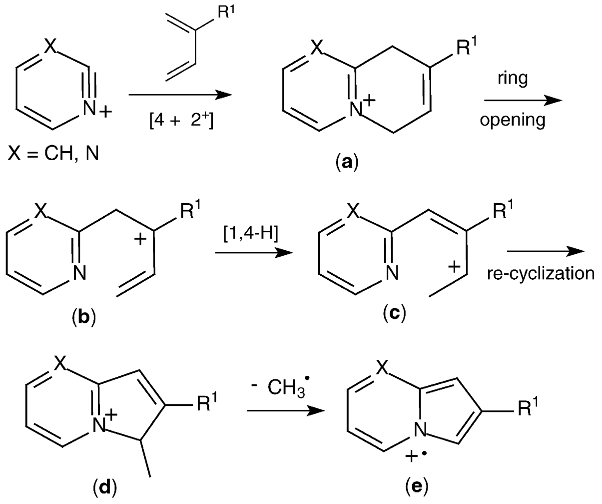


Fig. 5. Product ion mass spectra for the reaction of the 2-pyridyl cation with 1,3-butadiene. Note the abundant product ion of *m*/*z* 117, which has been identified (by comparison with the authentic ion) to be ionized indolizine. Adapted from reference [45].

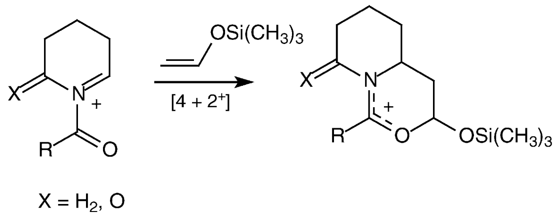


Scheme 23.

as high as 125.9 kcal/mol for that shown in Fig. 5), ions d then lose a methyl radical to form ions e as the observed major products, that is, the ionized indolizines.

3.5. Iminium and immonium ions

Nature and chemists use widely the Mannich reaction to form new carbon–carbon bonds via addition of electrophilic iminium and *N*-acyliminium ions [47] to enols or enolates. Solvated *N*-acyliminium ions are also one of the most thoroughly studied and widely used class of imino dienophiles [48]. We [49] have recently found that gaseous cyclic *N*-acyl and *N*,*N*-diacyliminium ions with endocyclic carbonyl groups, for which the *s-cis* conformation is favored, participate as heterodienophiles in polar [$4^+ + 2$] cycloadditions with silyl enol ethers (Scheme 24). For endocyclic analogs, however, C2-addition dominates.



Scheme 24.

Brenna and co-workers [50] have recently proposed a new method to determine double bond position in fatty acid methyl esters using acetonitrile CI tandem mass spectrometry. MS/MS and isotopic labeling experiments indicate that the (1-methyleneimino)-1-ethenylium ion, formed upon self-reactions of acetonitrile, undergoes [$2^+ + 2$] cycloaddition across the double bond of the neutral reactant. When this nascent complex dissociates, two fragment ions α and ω arise from loss of either the hydrocarbon or methyl ester end. These fragment ions are diagnostic for the double bond position, and possible mechanisms for their formation have been suggested, such as that for the α ions shown in Scheme 25.

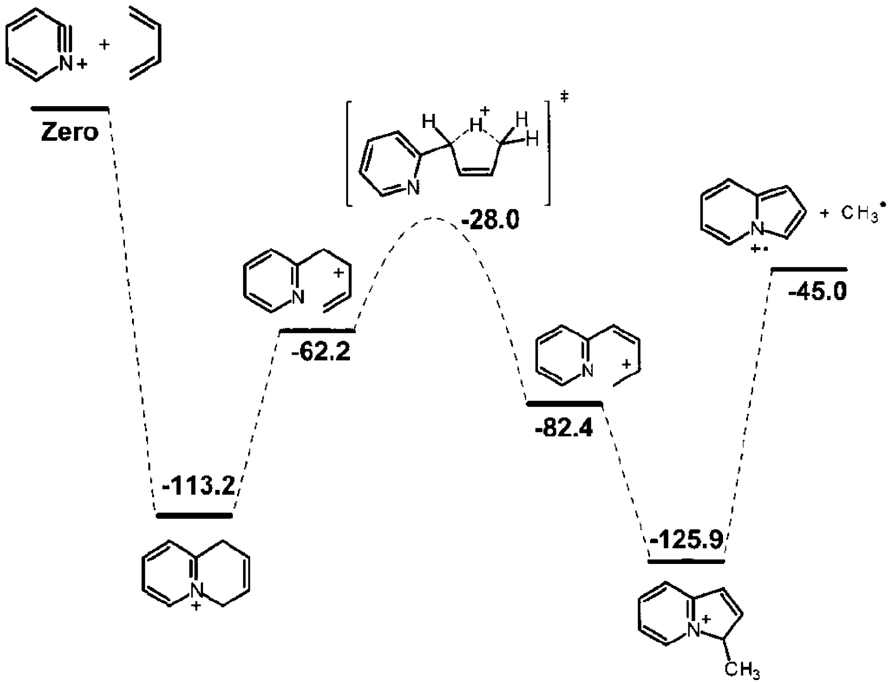
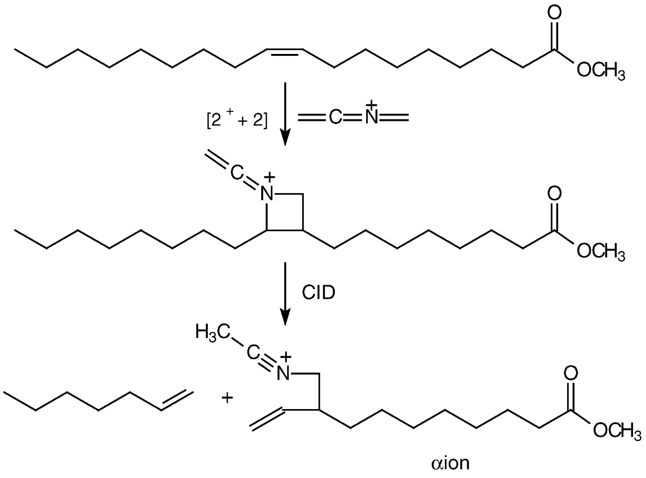
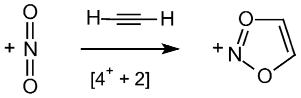


Fig. 6. Potential energy diagram from MP2/6-31G(d,p)//6-311G(d,p) calculations for the reaction of the 2-pyridyl cation with 1,3-butadiene. Energies are given in kcal/mol. Note that the cycloadduct arising from [$4 + 2^+$] cycloaddition is predicted to be far more stable than the acyclic adduct expect to arise from simple nucleophilic addition at C2. The high energy content of the cycloadduct induces ring-contraction followed by the loss of a methyl radical to form ionized indolizine. Reproduced with permission from reference [45].



Scheme 25.

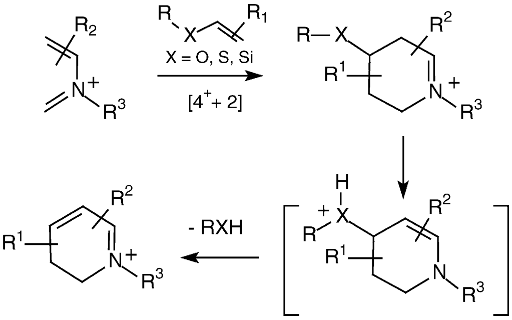


Scheme 26.

Troiani and co-workers [51] observed interesting 1,3-dipolar cycloadditions for the gaseous nitronium ion $O{=}N^{+}{=}O$ in reactions with acetylene (Scheme 26) and ethylene. The cycloadduct formed with acetylene has aromatic character and is therefore highly stabilized with respect to that with ethylene.

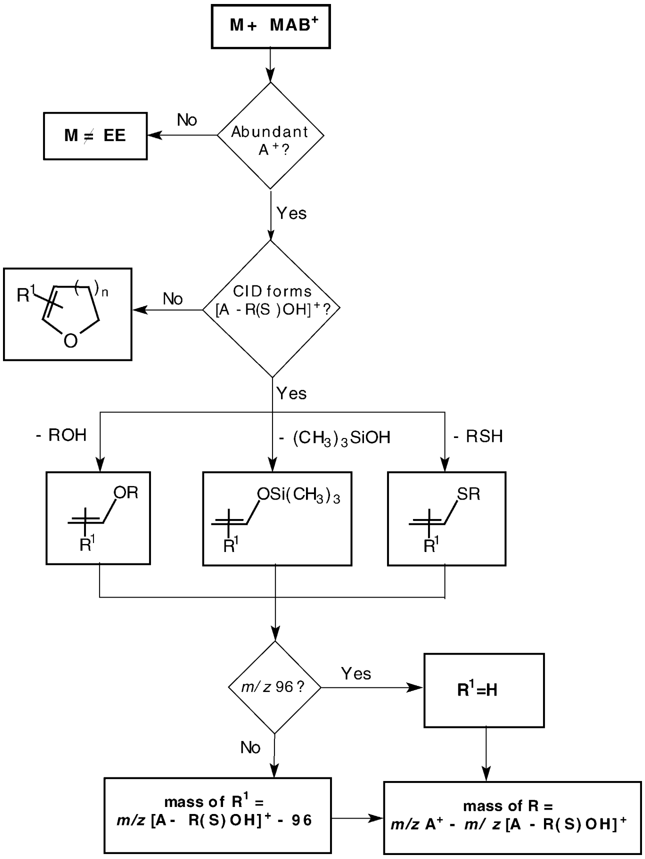
Azabutadienes are used vastly in the synthesis of nitrogen heterocyclics via inverse electron demand Diels–Alder cycloadditions [1]. To enhance electron deficiency and therefore to improve reactivity toward neutral or electron-rich dienophiles, protonated or cationized azabutadienes are commonly used in polar $[4^{+}+2]$ cycloadditions in solution [52]. We reported the first gas-phase polar $[4^{+}+2]$ cycloaddition of an azabutadiene, that of the prototype *N*-protonated 2-azabutadiene with ethyl vinyl ether, and suggested its potential analytical and structural application for the analysis of enol ethers [53].

We [54] latter found that the gaseous *N*-methyl-2-azabutadienyl cation (MAB^{+}) reacts similarly, readily and more generally with alkyl, silyl and thio-EEs (Scheme 27). The nascent cycloadducts are generally stable and observed as major products, and CID of the cycloadducts of acyclic EEs occurs competitively by retrocycloaddition and by the *functional-group* characteristic loss of either ROH, $(CH_3)_3SiOH$, or RSH (RXH in Scheme 27). Cycloadducts of acyclic EEs that bear no double bond substituents also form upon RXH loss a characteristic fragment ion of *m*/*z* 96. For the cycloadducts of EEs bearing double-bound substituents (R^1), the fragment ion arriving from RXH loss displays a mass shift that corresponds to the mass of R^1. Endocyclic EEs also react readily by MAB^{+} cycloaddition, but unless affected by ring substituents, the dissociation of their cycloadducts is dominated by RDA reaction. Detailed structural information (functional-group screening plus masses of substituents) of EEs and analogues is therefore provided, and positional isomers are easily distinguished.



Scheme 27.

The diagram of Scheme 28 was then proposed by us [54] for structural analysis of EEs and analogues using selective ion/molecule reactions with MAB^{+} followed by CID of the intact cycloadducts A^{+}. The logic of such diagram is the following: if the neutral reactant molecule (M) fails to readily form A^{+}, then M is unlikely to belong to the EE class. If M readily forms A^{+}, but, if upon CID, A^{+} fails to form the characteristic $[A - RO(S)H]^{+}$ fragment dissociating instead only by RDA, then M is classified as a cyclic EE. If alcohol (ROH, Fig. 7), silylol $[(CH_3)_3SiOH]$ (Fig. 8), or mercaptan



Scheme 28.

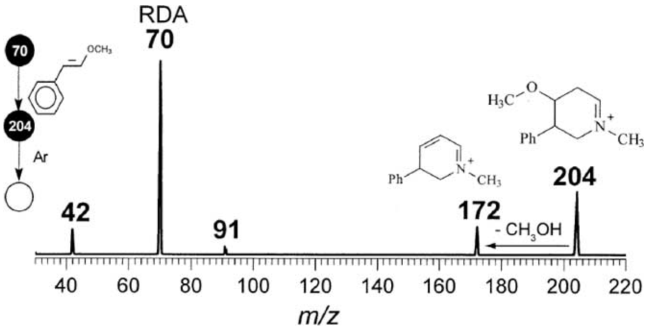


Fig. 7. Triple stage (MS^3) sequential product ion mass spectrum for CID of the polar [4 + 2^+] cycloadduct of the methyl 2-azabutadienyl cation (MAB^+) with methoxy styrene. Note the *functional-group* characteristic loss of CH_3OH of 32 u (from a methyl EE) to form the diagnostic ion of *m/z* 172 (76 u mass shift from *m/z* 96 which indicates a phenyl substituent at the double bond). Reproduced with permission from reference [54].

(RSH) loss is observed with their characteristic masses, then M is classified either as an alkyl (or aryl) EE, silyl EE, or thio-EE, respectively. If RO(S)H loss forms *m/z* 96 (Fig. 7), then M bears no double bond substituent ($R^1 = H$); hence M is classified as a *vinyl* (thio)EE. If otherwise, a substituent is present at the double bond, and the mass of R^1 is calculated from the observed mass shift of $[A{-}RO(S)H]^+$, that is: *m/z* $[A{-}RO(S)H]^+{-}96$ (Fig. 8). Finally, the mass of R, the O- or S-substituent, is simply calculated as: *m/z* A^+ − *m/z* $[A{-}RO(S)H]^+$.

We [55] also tested the generality of intrinsic polar [4^+ + 2] cycloaddition reactivity with EEs for a number of gaseous 2-azabutadienyl cations. Cycloaddition with ethyl vinyl ether occurs readily for all (eight) of such ions tested and, with the only exception of those from the *N*-acyl 2-azabutadienyl cations (*N*-acyl imminium ions), the cycloadducts dissociate readily upon CID both by RDA and by a characteristic neutral loss of an ethanol (46 u) molecule. Ethanol loss from the intact polar [4^+ + 2] cycloadduct functions therefore as a structure diagnostic test: 72 u neutral gain followed by 46 u neutral loss, that is, as a combined ion/molecule reaction plus CID "signature" for *N*-H, *N*-alkyl and *N*-aryl 2-azabutadienyl cations. The two *N*-acyl imminium ions tested are exceptional as they form intact cycloadducts with ethyl vinyl ether which dissociate exclusively by the retroaddition (RDA) pathway.

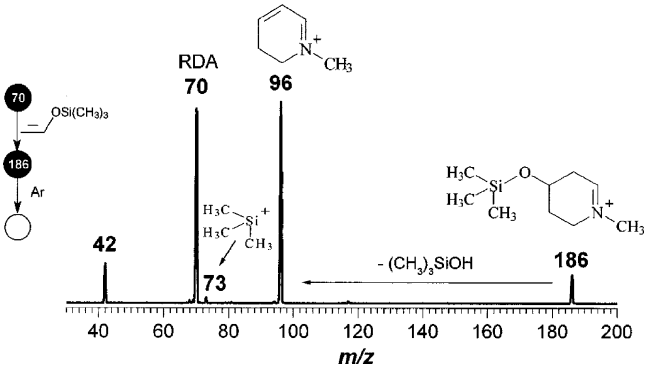
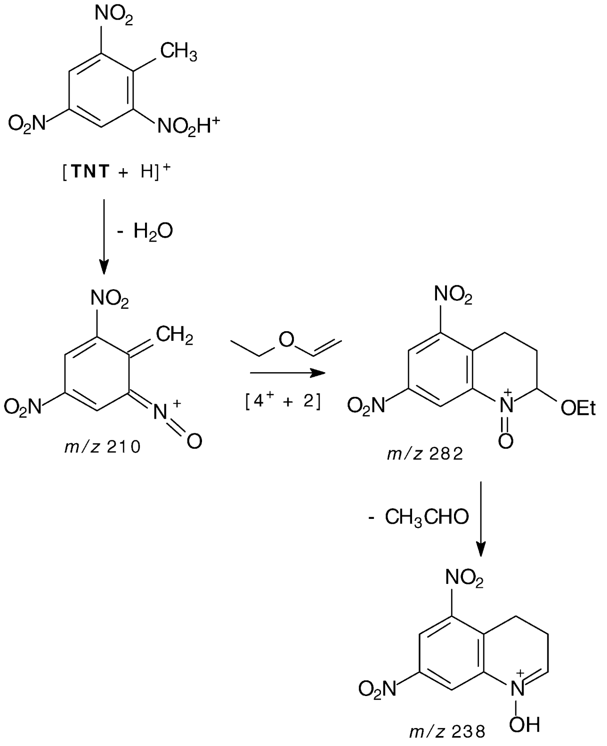


Fig. 8. Triple stage (MS^3) sequential product ion mass spectrum for CID of the polar [4 + 2^+] cycloadduct of the methyl 2-azabutadienyl cation (MAB^+) with vinyloxy trimethylsilane. Note the *functional-group* characteristic loss of $(CH_3)_3SiOH$ of 90 u (from a trimethylsilyl EE) to form the diagnostic ion of *m/z* 96 (no double bonds substituents). Reproduced with permission from reference [54].

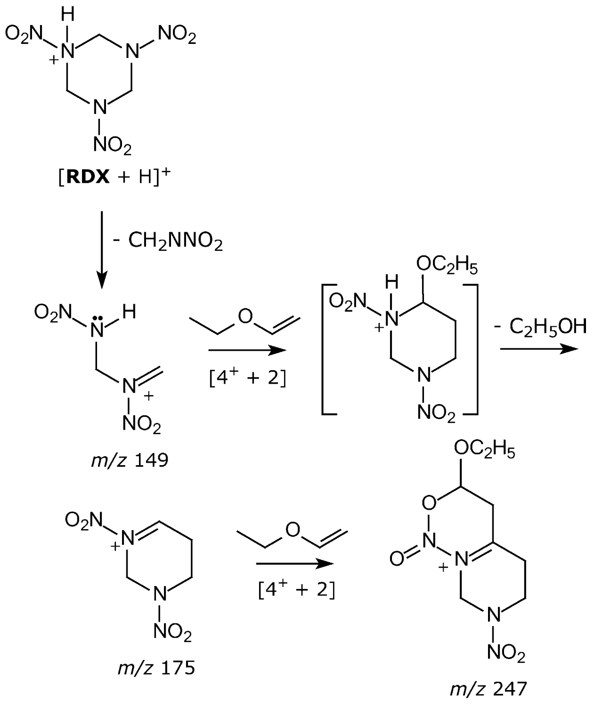


Scheme 29.

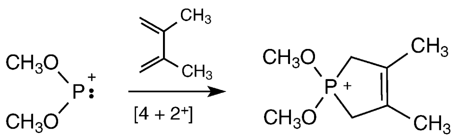
Cooks and co-workers have recently applied structure selective cycloadditions with ethyl vinyl ether for the secure detection of the explosives trinitrotoluene (TNT) and hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) [56]. Major electron and chemical ionization fragment ions of both TNT and RDX were selected for reaction. The fragment ion of *m/z* 210 from TNT undergoes cycloaddition with ethyl vinyl ether to form an oxa-iminium ion of *m/z* 282, which dissociates by acetaldehyde loss to form a quinolynium ion of *m/z* 238 (Scheme 29). The fragment ion of *m/z* 149 from RDX also undergoes cyloaddition with ethyl vinyl ether, and the nascent cycloadduct promptly loses an ethanol molecule to form a nitro-iminium ion of *m/z* 175. A second cycloaddition with ethyl vinyl ether occurs for this ion, and forms now a stable cycloadduct of *m/z* 247 (Scheme 30).

3.6. Phosphorous cations

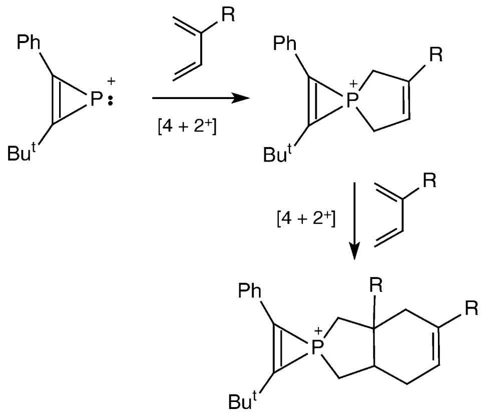
The presence of a vacant π orbital and a lone electron pair on phosphorous confers to the amphoteric phosphenium ions ($R_2P{:}^+$) high reactivity on organic substrates [57]. In solution, most reactions have been reported for phosphenium ions bearing at least one amino group which impart the



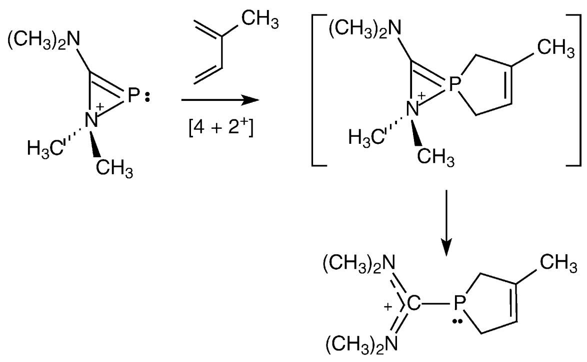
Scheme 30.



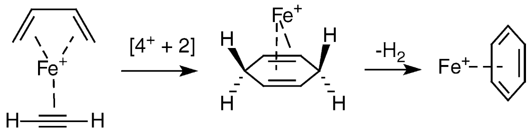
Scheme 31.



Scheme 32.



Scheme 33.



Scheme 34.

necessary thermodynamic stability. In the gas phase, such stabilization is not necessary, and Morizur and co-workers [58] have observed that the phosphenium ion $P(OCH_3)_2^+$ is long-lived, and reacts extensively by polar $[4 + 2^+]$ chelotropic cycloaddition (a form of cycloaddition across dienes and analogues with formation of two new σ-bonds to a single atom [3]) with 2,3-dimethylbutadiene to form a cyclic phospholenium ion (Scheme 31). This reactivity is similar to that observed in solution [56] for the nitrogen analogue ion $P(NCH_3)_2^+$.

Similarly to $P(OCH_3)_2^+$ in reactions with 2,3-dimethylbutadiene, we [59] also observed that a gaseous phos-

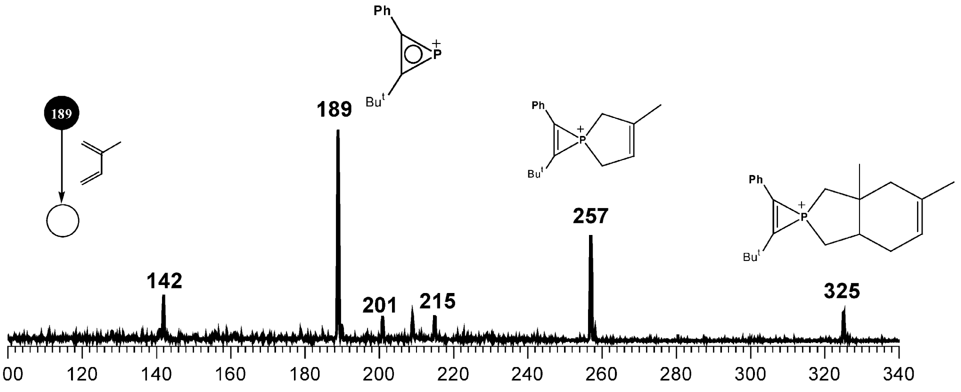
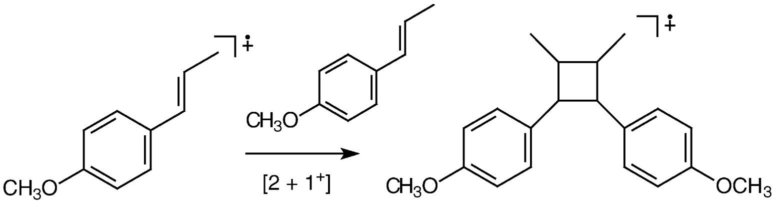


Fig. 9. Product ion (MS^2) mass spectrum for reactions of the 3-dimethylamino-1,1-dimethyl-1*H*-azaphosphiren-1-ium ion of *m/z* 189 with isoprene. Note the mono (*m/z* 257) and double $[4 + 2^+]$ cycloadducts (*m/z* 325). Adapted from reference [59].



Scheme 35.

phirenylium ion reacts readily with butadiene, isoprene (Fig. 9), 1-acetoxybutadiene, and with Danishefsky's diene (1-methoxy-3-silyloxybuta-1,3-diene), by mono (and double) $[4 + 2^+]$ cycloaddition at phosphorus to generate novel *P*-spiro bicyclic phosphonium ions (Scheme 32).

Recently, we [60] also observed that the first member of the hitherto unknown class of azaphosphirenium ions, and the first *N*,*P*-analogue of the aromatic cyclopropenyl cation, undergoes polar $[4 + 2^+]$ cycloaddition with isoprene, followed by spontaneous ring-opening (Scheme 33). These gas-phase chelotropic cycloadditions are analogous to those documented for phosphenium ions in solution [56].

3.7. Cycloadditions mediated by Fe^+

As shown mainly by Jacobson and co-workers and Schwarz and co-workers [61], Diels–Alder cycloadditions of dienes with unactivated alkynes and alkenes can be mediated by gaseous bare transition–metal cations M^+ (most efficiently by Fe^+ as demonstrated by Freiser and co-workers [62]). The reaction proceeds by fast H_2 loss to form aromatic rings (Scheme 34).

4. Polar cycloadditions monitored in solution by MS

With the development of the electrospray ionization (ESI) [63] and the atmospheric pressure chemical ionization technique [64], reactions can now also be investigated directly in solution by MS. ESI and APCI have been shown to gently transfer, for MS analysis, either ionic or neutral reactants, transient intermediates, and products of such reactions directly from solution to the gas-phase (for some recent examples see) [65]. Examples of such powerful approach are also found for cycloadditions, such as the polar radical cation $[2 + 1^+]$ cycloaddition of *trans*-anetohole (Scheme 35), investigated recently by Metzger and co-workers [66] using both ESI–MS and APCI–MS with the detection and characterization of transient radical cation intermediates.

5. Final remarks

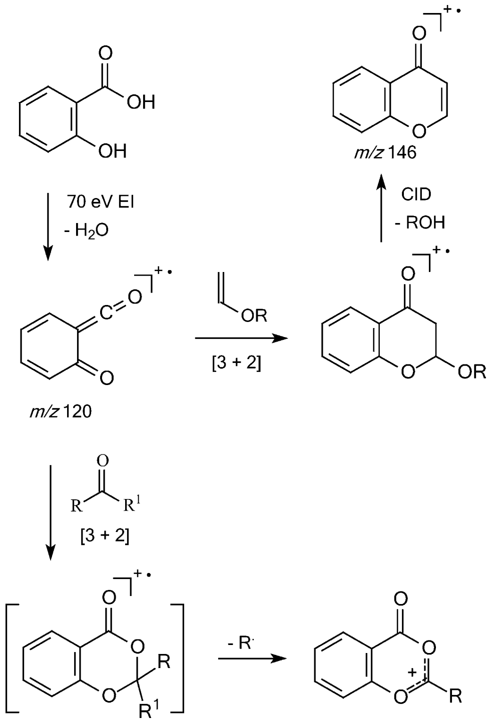
The dilute gas-phase environment of mass spectrometers provides a versatile and convenient medium in which chemists can form a great variety of solvent- and counterion-free ions, and to explore their reactivity in polar cycloadditions involving either even- or odd-electron ions. A variety of such reactions has been investigated by MS, the intrinsic cyclization reactivity of the ionic reactants determined, mechanistic aspects revealed, analytical and synthetic applications found, and new reactions described for the first time in MS environments. Additionally, the revolutionary ESI and APCI techniques now allow the unique opportunity to monitor cycloadditions by MS directly from solution, or even to perform these diagnostic reactions in-source, under atmospheric pressure ESI and APCI gas-phase environments [67].

Note added in proof

Very recently, the formation of a long-lived ionized α-oxoketene has been demonstrated, and its gas-phase polar cycloaddition reactivity investigated. α-Oxoketenes are highly reactive, usually transient and important building blocks in organic synthesis [68]. The cyclic short-lived *o*-quinonoid ketene (Scheme *x*) has been the subjected of much investigation, with many reports on attempts to perform its spectral characterization and chemical trapping [68]. For α-oxoketenes with 1,3-oxadiene systems, [2 + 2] cycloadditions so common for other ketenes are often overridden by [4 + 2] cycloadditions with dienophiles. We [69] have recently found that ionized *o*-quinonoid ketene of *m*/*z* 120 is easily formed from EI of salicylic acid followed by water loss, and that this long-lived gaseous ion can be "trapped" via a series of very efficient polar [3 + 2] cycloaddition reactions with enol ethers and ketones. The nascent cycloadducts with enol ethers are quite stable, and dissociate upon CID mainly by ROH loss to form likely ionized 4*H*-chromen-4-one of *m*/*z* 146 (Scheme 36). The nascent cycloadducts with activated ketones dissociates rapidly by the loss of an alkyl group to form resonance stabilized cyclic dioxonium ions.

Acknowledgements

I am greatly indebted to all co-authors of our gas-phase polar cycloaddition studies herein described. In particular, I thank Brian, Chrys and Graham [16] for sharing with me the efforts to perform my first gas-phase polar cycloaddition with the $C_4H_4^{+\bullet}$ cyclobutadiene ion. I am also sincerely thankful to the editor (for support) and reviewers (for comments) involved in my 5-year long "endeavor" to publish the



Scheme 36.

first report on a 1,3-polar cycloaddition of an α-distonic ion. The indispensable but nowadays rare financial support for fundamental MS studies from the Brazilian Science Foundations FAPESP and CNPq must also be greatly acknowledged.

References

[1] W. Carruthers, Cycloadditon Reactions in Organic Synthesis, Pergamon, 1990.
[2] O. Diels, K. Alder, Justus Liebigs Ann. Chem. 460 (1928) 98.
[3] IUPAC Compendium of Chemical Terminology, second ed., 1997.
[4] R.R. Schmidt, Angew. Chem. Int. Edit. 12 (1973) 212.
[5] N.L. Bauld, D.J. Bellville, B. Harirchian, K.T. Lorenz, R.A. Pabon Jr., D.W. Reynolds, D.D. Wirth, H.-S. Chiou, B.K. Marsh, Acc. Chem. Res. 20 (1987) 371.
[6] (a) C. Dass, Mass Spectrom. Rev. 9 (1990) 1;
(b) S. Gronert, Chem. Rev. 101 (2001) 329;
(c) D. Kuck, M. Mormann, in: The Chemistry of Dienes and Polyenes, vol. 2, Rappoport, Z., 2002, Wiley.
[7] N. Heinrich, W. Koch, J.C. Morrow, H. Schwarz, J. Am. Chem. Soc. 110 (1988) 6332.
[8] C.L. Wilkins, M.L. Gross, J. Am. Chem. Soc. 93 (1971) 895.
[9] R. van Doorn, N.M.M. Nibbering, A.J.V. Ferrer-Correia, K.R. Jennings, Org. Mass Spectrom. 13 (1978) 729.
[10] M. Vairamani, U. Mirza, R. Srinivas, Mass Spectrom. Rev. 9 (1990) 253.
[11] J. Einhorn, J.M. Duffault, H. Virelizier, J.C. Tabet, Rapid Commun. Mass Spectrom. 2 (1988) 112.
[12] A. Colorado, D.J. Barket, J.M. Hurst, P.B. Shepson, Anal. Chem. 70 (1998) 5129.
[13] (a) G. Bouchoux, J.-Y. Salpin, Rapid Commun. Mass Spectrom. 8 (1994) 325;
(b) G. Bouchoux, M.T. Nguyen, J.-Y. Salpin, J. Phys. Chem. 104 (2000) 5778.
[14] H.-F. Grützmacher, A. Barkow, Acta Chem. Scand. 51 (1997) 619.
[15] H. Becker, G. Javahery, S. Petrie, D.K. Bohme, J. Phys. Chem. 98 (1994) 5591.
[16] B.J. Shay, M.N. Eberlin, R.G. Cooks, C. Wesdemiotis, J. Am. Soc. Mass Spectrom. 3 (1992) 518.
[17] D.J. Goerbbert, X. Liu, P.G. Wenthold, J. Am Soc. Mass Spectrom. 15 (2004) 114.
[18] (a) S. Hammerum, Mass Spectrom. Rev. 7 (1988) 123;
(b) K.M. Stirk, M.L.K. Kiminkinen, H.I. Kenttämaa, Chem. Rev. 92 (1992) 1649.
[19] B.F. Yates, W.J. Bouma, L. Radom, Tetrahedron 42 (1986) 6225.
[20] L.A.B. Moraes, M.N. Eberlin, J. Am. Chem. Soc. 120 (1998) 11136.
[21] M.N. Eberlin, A.E.P.M. Sorrilha, F.C. Gozzo, R. Pimpim, J. Am. Chem. Soc. 119 (1997) 3550.
[22] C. Lange, Org. Mass Spectrom. 28 (1993) 1285.
[23] P. Mourgues, H.E. Audier, S. Hammerum, Rapid Commun. Mass Spectrom. 8 (1994) 53.
[24] P. Gerbaux, Y.V. Haverbeke, R. Flammang, J. Am. Soc. Mass Spectrom. 14 (2003) 241.
[25] G.A. Olah, V.P. Reddy, G.K.S. Prakash, Chem. Rev. 92 (1992) 69.
[26] R.W. Holman, J. Plocica, L. Blair, D. Giblin, M.L. Gross, J. Phys. Org. Chem. 14 (2001) 17.
[27] (a) M.N. Eberlin, Mass Spectrom. Rev. 16 (1997) 113;
(b) M.N. Eberlin, Mass Spectrom. Rev., submitted for publication.
[28] M.N. Eberlin, R.G. Cooks, J. Am. Chem. Soc. 115 (1993) 9226.
[29] E.C. Meurer, M.N. Eberlin, J. Mass Spectrom. 37 (2002) 146.
[30] E.C. Meurer, L.A.B. Moraes, M.N. Eberlin, Int. J. Mass Spectrom. 212 (2001) 445.
[31] M.N. Eberlin, T.K. Majumdar, R.G. Cooks, J. Am. Chem. Soc. 114 (1992) 2884.
[32] V.J. Juliano, F.C. Gozzo, M.N. Eberlin, C. Kascheres, Anal. Chem. 68 (1996) 1328.
[33] M. Sharifi, J. Einhorn, Int. J. Mass Spectrom. 190–191 (1999) 253.
[34] M.N. Eberlin, N.H. Morgon, S.S. Yang, B.J. Shay, R.G. Cooks, J. Am. Soc. Mass Spectrom. 6 (1995) 1.
[35] M.N. Eberlin, M. Basher, J.M. Riveros, J. Mass Spectrom, submitted for publication.
[36] F.C. Gozzo, A.E.P.M. Sorrilha, M.N. Eberlin, J. Chem. Soc. Perkin Trans. (1996) 587.
[37] L. Lu, S.S. Yang, Z. Wang, R.G. Cooks, M.N. Eberlin, J. Mass Spectrom. 30 (1995) 581.
[38] A.D. Lemos, R. Sparrapan, M.N. Eberlin, J. Mass Spectrom. 38 (2003) 305.
[39] J.S. Brodbelt, Mass Spectrom. Rev. 16 (1997) 91.
[40] T. Keough, Anal. Chem. 54 (1982) 2540.
[41] L. Ma, Z. Liu, W. Wang, X. Guo, S. Liu, J. Phys. Chem. A 103 (1999) 8634.
[42] M.W.E.M. van Tilborg, R. van Doorn, N.M.M. Nibbering, Org. Mass Spectrom. 15 (1980) 152.
[43] F.C. Gozzo, M.N. Eberlin, J. Org. Chem. 64 (1999) 2188.
[44] T. Kauffmann, Angew. Chem. 77 (1965) 557.
[45] R. Sparrapan, M.A. Mendes, M. Carvalho, M.N. Eberlin, Chem. Eur. J. 6 (2000) 321.
[46] M.N. Eberlin, R. Augusti, J. Mass Spectrom., submitted for publication.
[47] M.G.M. D'Oca, L.A.B. Moraes, R.A. Pilli, M.N. Eberlin, J. Org. Chem. 66 (2001) 3854.
[48] S.B. Needleman, M.C. Chang-Kuo, Chem. Rev. 62 (1962) 45.
[49] D.M. Tomazela, L.A.B. Moraes, M.G.M. D'Oca, R.A. Pilli, M.N. Eberlin, J. Org. Chem. 67 (2002) 4652.
[50] (a) C.K. Van Pelt, J.T. Brenna, Anal. Chem. 71 (1999) 1981;
(b) C.K. Pelt, B.K. Carpenter, J.T. Brenna, J. Am. Soc. Mass. Spectrom. 10 (1999) 1253.
[51] F. Bernardi, F. Cacace, G. Petris, F. Pepi, I. Rossi, A. Troiani, Chem. Eur. J. 6 (2000) 537.

[52] D.L. Boger, S.N. Weinreb, in: H.H. Wasserman (Ed.), Hetero Diels–Alder Methodology in Organic Synthesis, New York, Academic Press, 1987.

[53] R. Augusti, F.C. Gozzo, L.A.B. Moraes, R. Sparrapan, M.N. Eberlin, J. Org. Chem. 63 (1998) 4889.

[54] E.C. Meurer, L.A.B. Moraes, M.N. Eberlin, Int. J. Mass Spectrom. 212 (2001) 445.

[55] E.C. Meurer, R. Sparrapan, M.N. Eberlin, J. Mass Spectrom. 38 (2003) 1075.

[56] E.C. Meurer, H. Chen, L. Riter, I. Cotte-Rodriguez, M.N. Eberlin, R.G. Cooks, Chem. Commun. (2004) 40.

[57] (a) A.H. Cowley, R.A. Kemp. Chem. Rev. 85 (1985) 367;
(b) S.E. Solovieva, M. Gruner, I.S. Antipin, W.D. Habicher, A.I. Konovalov, Org. Lett. 3 (2001) 1299.

[58] S. Gevrey, M.-H. Taphanel, J.-P. Morizur, J. Mass Spectrom. 33 (1998) 399.

[59] A.A. Sabino, M.N. Eberlin, L.A.B. Moraes, K.K. Laali, Org. Biomol. Chem. 1 (2003) 395.

[60] L.A.B. Moraes, M.N. Eberlin, K.K. Laali, Organometallics 20 (2001) 4863.

[61] (a) R. Bakhtiar, J.D. Drader, D.B. Jacobson, J. Am. Chem. Soc. 114 (1992) 8304;
(b) K. Schroeter, C.A. Schalley, R. Wesendrup, D. Schöder, H. Schwarz, Organometallics 16 (1997) 986.

[62] Q. Chen, C. Sioma, S.Z. Kan, B.S. Freiser, Int. J. Mass Spectrom. 180 (1998) 231.

[63] J.B. Fenn, M. Mann, C.K. Meng, S.F. Wong, C.M. Whitehouse, Science 246 (1989) 64.

[64] E.C. Huang, T. Wachs, J.J. Conboy, J.D. Henion, Anal. Chem. 62 (1990) 713.

[65] (a) C. Hilderling, C. Adlhart, P. Chen, Angew. Chem. Int. Ed. 37 (1998) 2685;
(b) P. Chen, Angew. Chem. Int. Ed. 42 (2003) 2832;
(c) A.A. Sabino, A.H.L. Machado, C.R.D. Correia, M.N. Eberlin, Angew. Chem. Int. Ed. 43 (2004) 2514;
(d) E.C. Meurer, L.S. Santos, R.A. Pilli, M.N. Eberlin, Org. Lett. 5 (2003) 1391;
(e) S.H. Choi, R.B. Cooley, A.S. Hakemian, Y.C. Larrabee, R.C. Bunt, S.D. Maupas, J.G. Muller, C.J. Burrows, J. Am. Chem. Soc. 126 (2004) 591;
(f) D.I. Schuster, J.R. Cao, N. Kaprinidis, Y.H. Wu, A.W. Jensen, Q.Y. Lu, H. Wang, S.R. Wilson, J. Am. Chem. Soc. 118 (1996) 5639.

[66] (a) S. Meyer, J.O. Metzger, Anal. Bioanal. Chem. 377 (2003) 1108;
(b) S. Meyer, R. Koch, J.O. Metzger, Angew. Chem. Int. Ed. 42 (2003) 4700.

[67] E.C. Meurer, A.A. Sabino, M.N. Eberlin, Anal. Chem. 75 (2003) 4701.

[68] C. Wentrup, W. Heilmayer, G. Kollenz, Synthesis 343 (1994) 1219.

[69] M.N. Eberlin, L.A.B. Moraes, J. Mass Spectrom., submitted for publication.