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# Polar [4 + 2<sup>+</sup>] Diels–Alder Cycloaddition to Nitrilium and Immonium Ions in the Gas Phase: Applications of Multiple Stage Mass Spectrometry in a Pentaquadrupole Instrument

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Multiple stage MS<sup>2</sup> and MS<sup>3</sup> mass spectrometric experiments, performed using a pentaquadrupole instrument, are employed to explore the gas-phase ion–molecule chemistry of several nitrilium [R–C≡N<sup>+</sup>–H (1), R–C≡N<sup>+</sup>–CH<sub>3</sub> (2), and H–C≡N<sup>+</sup>–C<sub>2</sub>H<sub>5</sub> (3)] as well as immonium ions RR<sup>1</sup>C=N<sup>+</sup>R<sup>2</sup>R<sup>3</sup> (4) with the neutral diene isoprene. Polar [4 + 2<sup>+</sup>] Diels–Alder cycloaddition is observed for nitrilium ions when the energy gap between the lowest unoccupied molecular orbital (LUMO) of the ion and the highest occupied molecular orbital (HOMO) of the isoprene is small and the competing proton transfer reaction is endothermic. Thus, C-protonated methyl isonitrile H–C≡N<sup>+</sup>–CH<sub>3</sub> (2a) and its higher homolog H–C≡N<sup>+</sup>–C<sub>2</sub>H<sub>5</sub> (3a) form abundant [4 + 2<sup>+</sup>] cycloadducts with isoprene, but several protonated nitriles 1 do not; instead they show exothermic proton transfer as the main ion–molecule reaction. Replacement of the methyne hydrogen in 2a by a methyl, ethyl, or phenyl group (2b–d) raises the LUMO–HOMO gap, which greatly decreases the total yield of ion–molecule products and precludes cycloaddition. On the other hand, the electron-withdrawing acetyl and bromine substituents in 2e and 2f substantially lower the LUMO energy of the ions and cycloaddition reaction occurs readily. The simplest member of the immonium ion series, CH<sub>2</sub>=NH<sub>2</sub><sup>+</sup> (4a), reacts readily by cycloaddition, whereas alkyl substitution on either the carbon or nitrogen (4b–f) dramatically lowers the overall reactivity, which substantially decreases or even precludes cycloaddition. In strong contrast, the *N*-phenyl (4g) and *N*-acetyl (4h) ions and the *N*-vinyl-substituted immonium ion, *N*-protonated 2-aza-butadiene (4i), react extensively with isoprene, mainly by [4 + 2<sup>+</sup>] cycloaddition. However, the isomeric C-vinyl-substituted ion (4j) displays only modest reactivity in both the proton-transfer and the cycloaddition channels.

Collision-induced dissociation (CID) of the cycloadducts performed by on-line MS<sup>3</sup> experiments demonstrates that they are covalently bound and supports their assignments as cycloaddition products. Retro Diels–Alder fragmentation is a major process for cycloadducts of both the immonium and the nitrilium ions, but other fragmentation processes also are observed. The cycloadduct of 4a with butadiene displays CID fragmentation identical to that of the authentic ion produced by protonation of 1,2,3,6-tetrahydropyridine, which thus strengthens the [4 + 2<sup>+</sup>] cycloaddition proposal. AM1 calculations also support the formation of the [4 + 2<sup>+</sup>] cycloadducts, which are shown in several cases to be much more stable than the products of simple addition, that is, the ring-open isomers. (*J Am Soc Mass Spectrom* 1995, 6, 1–10)

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Gas-phase reactions of ions with neutral molecules have been known since the pioneering experiments of Thomson [1] and Dempster [2]. Mechanisms of formation of H<sub>3</sub><sup>+</sup>, I<sub>3</sub><sup>+</sup>, and H<sub>3</sub>O<sup>+</sup> [2, 3]

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and the earliest theory that described ion–molecule reactions [4] were published before 1940. In the 1950s improvements in vacuum technology and electronics supplied a more controlled environment in which to perform ion–molecule reactions, and since then the field has flourished [5]. The rate constants of thousands of ion–molecule reactions have been determined

[6], along with their temperature dependence [7], and these data have been used to obtain important thermodynamic values [8] such as bond energies, gas-phase proton affinities, and ionization energies. Ion-molecule reactions also provide important insights into solution chemistry by probing the intrinsic or solvent-free properties of ions and molecules. Gas-phase reactions have been used to resolve some long-standing problems; a classic case is that concerning the intrinsic relative acidities of amines [9a] and a more recent case is their use to determine the diastereomeric selectivity of hydride reductions in the absence of solvent or counterions [9b].

These types of studies can be carried out in a mass spectrometer ion source operated at sufficiently elevated pressures, and in this way many authors [10] have provided data that underpin our quantitative knowledge of solvation and clustering. Nevertheless, ambiguities exist in ion source studies with regard to the precursor ion(s) or the pathway(s) by which products are formed, and this has fueled the development of methods that use mass-selected ions. Several instruments have been employed for this purpose including flowing afterglow instruments with quadrupole mass filters for precursor ion selection [10], triple quadrupoles [11, 12] with a central reaction quadrupole, three-dimensional ion traps [13] that employ temporal mass selection, and multiple sector (and hybrid) instruments with collision cells floated so as to produce ion beams with a few volts of translational energy [14]. More recently, pentaquadrupole instruments have been introduced [15]. They employ an ion source, two reaction regions, and three mass filters, and so allow the study of reactions that occur in sequence in three separate regions and allow product identification by using three stages of mass analysis (vide infra). Each of the foregoing instruments has particular merits. The advantages of the pentaquadrupole mass spectrometer for ion-molecule studies are exemplified by specific and detailed information on the structures of ionic species or reaction mechanisms obtained by  $MS^3$  experiments that use scan modes that produce two- or three-dimensional mass spectra [16]. In addition, the instrument is simple to operate and minimizes precursor contamination problems.

Diels-Alder cycloadditions [17] are widely used in chemical synthesis. Most Diels-Alder reactions involve addition of a neutral diene to a dienophile, a process that is often enhanced by polar functional groups [17, 18]. In fact, even-electron cations [19] and radical cations [20] (generated in inert solvents) are both known to undergo Diels-Alder reactions, often in better yields than their neutral counterparts. Gas-phase cycloaddition reactions of cations also have been studied [21, 22]. New chemistry has emerged; for example, the 4-methoxy-cyclohexene radical cation has been formed in the gas phase by cycloaddition of vinyl methyl ether radical cations to 1,3-butadiene [22], a reaction that is not known in solution. Ionized phenyl-

tetralin has been synthesized by the cycloaddition of styrene radical cations to neutral styrene [22c] and the radical cation of cyclobutadiene is observed to undergo [2 + 2] and [4 + 2] cycloadditions with several neutral dienes [21a]. The even-electron acetyl cation  $CH_3-C\equiv O^+$  recently has been observed to form abundant [4 + 2<sup>+</sup>] cycloadducts with isoprene and several other "s-cis" conjugated dienes, and similar reactivity has been observed for its sulfur analog, the thioacetyl cation  $CH_3-C\equiv S^+$  [21b]. This work was extended [21c] to a larger set of acylium ions that contain several alkyl, aryl,  $\pi$ -electron-donating, and  $\alpha,\beta$ -unsaturated substituents, and the effects of such substituents on the cycloaddition reactivity, including regioselectivity, were studied by  $MS^2$  and  $MS^3$  experiments.

Nitrilium ions ( $R-C\equiv N^+-R^1$ ) and immonium ions ( $RR^1C=N^+R^2R^3$ ) are important and common ionic species in mass spectrometric experiments. In addition, many nitrilium ions occur in the stratosphere [23] and the lower atmosphere [24]. Although these ions have been encountered in the gas phase in many mass spectrometric experiments [25], little is known about their gas-phase ion-molecule chemistry. In solution, neutral nitriles and immonium ions have been used in several cycloaddition synthetic strategies [17]. Nitrilium ions of the type  $RC\equiv NH^+$  can be formed in solution, but their  $pK_a$  values are sufficiently high as to make their use in cycloaddition reactions impractical. The solution chemical behavior of immonium ions and the activating nature of the polar C-N bonds in both the nitrilium and immonium ions indicate that they might undergo gas-phase Diels-Alder cycloadditions with dienes. This article therefore describes a systematic study of the ion-molecule chemistry of a series of nitrilium and immonium ions in reactions with an "s-cis" conjugated diene, isoprene. The experiments were performed in the gas-phase environment by multiple stage mass spectrometric experiments, and the intrinsic effects of substitution on [4 + 2<sup>+</sup>] cycloaddition versus proton transfer, as well as on the overall reactivity of the ionic species, was examined. To help explain dramatic changes observed in chemical reactivity, frontier orbital theory [26] was applied: the corresponding energies of the frontier orbitals were calculated by the AM1 method [27].

## Experimental Section

The  $MS^2$  and  $MS^3$  experiments were performed using a custom-built pentaquadrupole mass spectrometer, which is described in detail elsewhere [15c]. This instrument consists of three mass-analyzing quadrupoles (Q1, Q3, Q5), typically operated at unit mass resolution, and two collision quadrupoles (Q2, Q4). Ions were created by 70-eV electron ionization or chemical ionization (CI). The Q1 mass-selected ion beam was allowed to react with isoprene in the collision cell Q2.

Nominally zero translational energy was used to facilitate ion-molecule reactions. The nature of the products generated on reaction with isoprene was investigated by using the MS<sup>3</sup> experiment known as the sequential product scan [16]. This spectrum was acquired by using Q3 for mass selection of the desired product ion, generated in Q2, and by performing collision-induced dissociation (CID) at 10-eV collision energy upon an argon target in Q4. The final quadrupole (Q5) was scanned to record the MS<sup>3</sup> spectrum. The pressures of the isoprene reactant gas and the argon collision gas were typically  $3 \times 10^{-5}$  torr (nominal), and when both gases were employed in the same experiment the total indicated pressure was typically  $8 \times 10^{-5}$  torr, as measured by an ionization gauge mounted on the housing that contains the collision quadrupoles. The ion beam attenuation due to argon in Q4 was typically 50%.

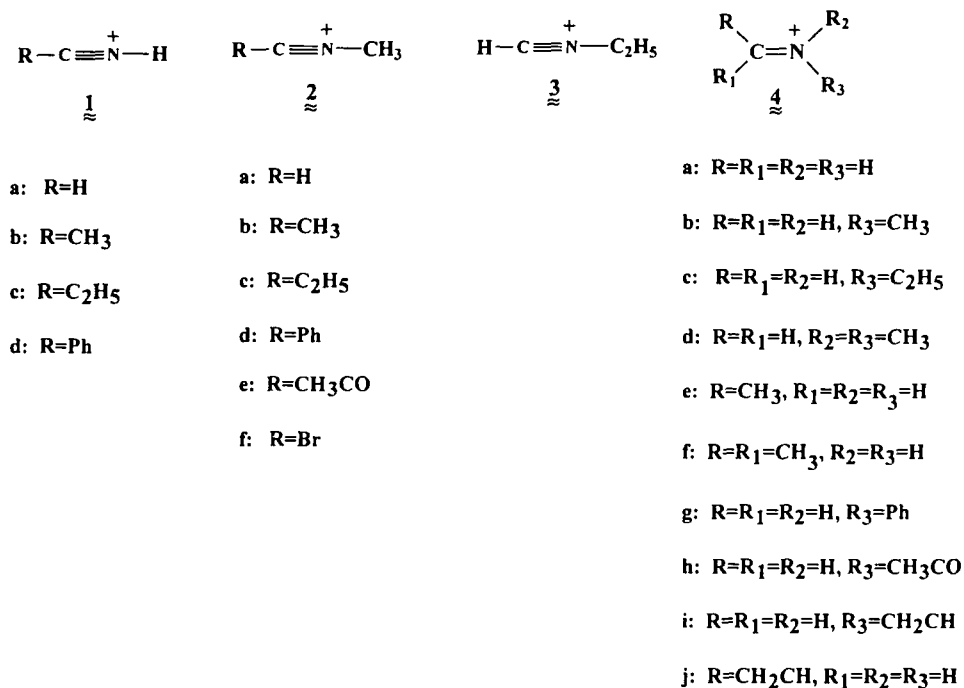
The reactant ions were generated as follows: ions **1a-d** by methane CI protonation of the corresponding nitriles, ions **2a-f** by CH<sub>3</sub><sup>+</sup> transfer to HCN and the corresponding nitriles during CH<sub>3</sub>I CI (AM1 predicts that the CH<sub>3</sub><sup>+</sup> affinity of acetyl nitrile (CH<sub>3</sub>-CO-C≡N) is 12.5 kcal/mol higher at the nitrogen when compared to that at the carbonyl oxygen). HCN was generated by reaction of a small amount of KCN with concentrated H<sub>2</sub>SO<sub>4</sub>. This procedure is dangerous and must be carried out with CARE! Ion **2a** also was generated by phenyl radical loss from *N*-benzylidenemethylamine (Ph-CH=N-CH<sub>3</sub>); ion **3** was generated by C<sub>2</sub>H<sub>5</sub><sup>+</sup> addition to the nitrogen atom of HCN by methane CI; ion **4a** was obtained by ethyl

radical loss from ionized *n*-propyl amine; ion **4b** was obtained by ethyl radical loss from ionized *N*-methylpropylamine; **4c** was obtained from methyl radical loss from ionized diethylamine; **4d** was obtained from hydrogen radical loss from ionized trimethylamine radical cation; **4e** and **4f** were generated from methyl and hydrogen radical loss from ionized isopropylamine, respectively; **4g** was generated by methyl radical loss from ionized *N*-ethyl-*N*-phenylamine; **4h** was obtained by CH<sub>4</sub> CI-protonation of *N*-acetylglycine and subsequent loss of water and CO; **4i** was obtained by C<sub>2</sub>H<sub>6</sub>N radical loss from ionized *N*-methyl piperazine [28]; **4j** was generated by hydrogen radical loss from ionized allyl amine. The samples were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as supplied except for a single liquid nitrogen freeze-thaw cycle used to remove noncondensable gases.

The AM1 calculations [27] were carried out using the MOPAC6 program [29]. Full geometry optimizations were performed for the calculation of Δ*H*<sub>f</sub><sup>o</sup> values and highest occupied molecular orbital (HOMO) as well as lowest unoccupied molecular orbital (LUMO) energies for isoprene and all ionic species. The keyword PRECISE was used for increased precision as suggested by Stewart and co-workers [30].

## Results and Discussion

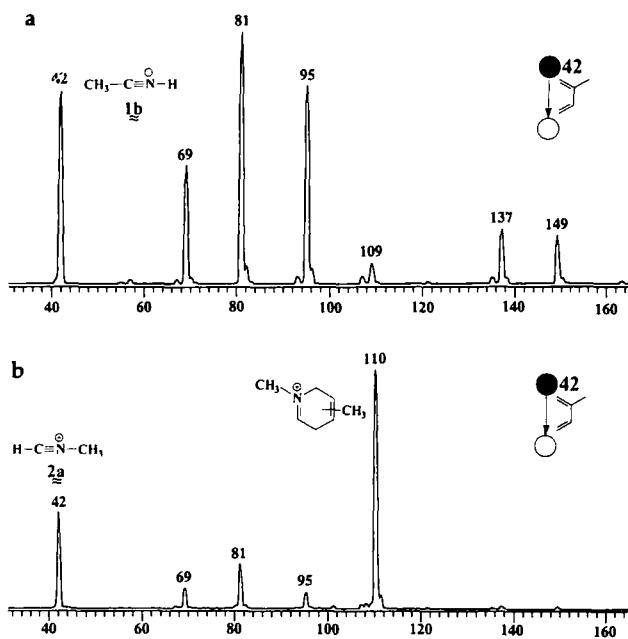
Gas-phase ion-molecule reactions were investigated for several mass-selected nitrilium (**1a-d**, **2a-f**, and **3**) and immonium ions (**4a-j**) (Scheme I) with the conjugated diene isoprene.



Scheme I. The structures of nitrilium and immonium ions investigated.

### Ion-Molecule Reaction Product Spectra

**Nitrilium ions 1** Figure 1a displays the MS<sup>2</sup> product spectrum for the reactions of ion **1b** with isoprene. A summary of this spectrum as well as of all the MS<sup>2</sup> product spectra recorded in this study is presented in Table 1. In this table, a measure of the overall reactivity of the ions given by the ratio of the abundances of all ionic products to that of the surviving reactant ion is also included. This is only a crude estimate because similar experimental conditions were applied for all ion-molecule reactions, but rigorous control of the reactant ion initial intensity or collision gas pressure was not achieved. This estimate, however, is useful to show the dramatic changes in reactivity observed within the homologous series. The ion-molecule reaction spectrum for ion **1b** does not produce the adduct ( $m/z$  110) and is entirely dominated by the products of proton transfer to isoprene ( $m/z$  69), namely the ions at  $m/z$  81, 93, 95, 107, 109, 135, 137, and 149. The origin of these ions as the products of reactions of protonated isoprene with neutral isoprene was established by separate MS<sup>2</sup> experiments [21a]. The great proclivity of ion **1b** to react with isoprene by proton transfer can be associated with the 12.2-kcal/mol exothermicity of this reaction (Table 2). All the other R—C≡N<sup>+</sup>—H nitrilium ions (**1a**, **1c**, and **1d**) display identical ion-molecule reactivity with isoprene and yield product spectra that are dominated by the proton transfer products (Table 1).



**Figure 1.** MS<sup>2</sup> product spectra for the reactions of mass-selected  $m/z$  42 ions with isoprene (a) Ion **1b** ( $\text{CH}_3\text{C}\equiv\text{NH}^+$ ) reacts extensively by proton transfer, a reaction that leads to a series of products, mainly  $m/z$  69, 81, 93, 95, 107, 109, 135, 137, and 149 (b) Ion **2a** ( $\text{HC}\equiv\text{N}^+-\text{CH}_3$ ) reacts mainly by  $[4+2^+]$  cycloaddition to form the corresponding product at  $m/z$  110, among the less abundant proton transfer products.

**Table 1.** Partial MS<sup>2</sup> ion-molecule spectra for the ion-molecule reactions of the nitrilium and immonium ions with isoprene

Ion	$m/z$	Ionic Products		Overall reactivity <sup>c</sup>
		Proton transfer RA <sup>a</sup> of $m/z$ 81 <sup>b</sup> (%)	Cycloadduct $m/z$ RA <sup>a</sup> (%)	
<b>1a</b>	28	100	96 None	3.0
<b>1b</b>	42	100	110 None	3.8
<b>1c</b>	56	100	124 None	4.2
<b>1d</b>	104	100	172 None	2.6
<b>2a</b>	42	22	110 100	3.3
<b>2b</b>	56	100	124 None	0.02
<b>2c</b>	70	100	138 None	0.03
<b>2d</b>	118	100	186 None	0.02
<b>2e</b>	84	12	152 100	1.2
<b>2f</b>	120	8	188 100	0.3
<b>3</b>	56	16	124 100	0.3
<b>4a</b>	30	15	98 100	3.2
<b>4b</b>	44	19	112 100	0.1
<b>4c</b>	58	65	126 100	0.04
<b>4d</b>	58	100	126 None	0.01
<b>4e</b>	44	100	112 None	0.01
<b>4f</b>	58	100	126 None	0.01
<b>4g</b>	106	4	174 100	0.8
<b>4h</b>	72	8	140 100	0.3
<b>4i</b>	56	8	124 100	2.4
<b>4j</b>	56	100	124 15	0.02

<sup>a</sup> Relative abundance, measured relative to the major peak, excluding the Q1 mass-selected ion

<sup>b</sup> Only the relative abundance of  $m/z$  81, the most abundant product of the proton transfer channel, is reported because the same set of secondary products (see text and Figure 1a) is observed throughout these experiments and there is little variation in their relative abundances

<sup>c</sup> Measured by the ratio of the sum of the abundance of all the ionic products to that of the preselected reactant ion. This is a crude measurement of reactivity (see text)

**Table 2.** Relevant thermodynamic data (kcal/mol)<sup>a</sup>

Neutral (M)	Ion (MH <sup>+</sup> )	PA	$\Delta\text{PA}^b$	$\Delta H_f^\circ$ Neutral	$\Delta H_f^\circ$ Ion
Isoprene	$\text{C}_5\text{H}_9^+$	200.4	—	18	183
$\text{CH}_3-\text{CN}$	<b>1b</b>	188.2	-12.12	18	195
$\text{CH}_3-\text{NC}$	<b>2a</b>	201.4 <sup>c</sup>	1.0	41	205
$\text{C}_2\text{H}_5-\text{CN}$	<b>1c</b>	192.6	-7.8	12.3	185
$\text{C}_2\text{H}_5-\text{NC}$	<b>3</b>	203.7	3.3	33.8	196
$\text{CH}_2=\text{NH}$	<b>4a</b>	225.7 <sup>c</sup>	25.3	38	178
$\text{CH}_2=\text{N}-\text{CH}_3$	<b>4b</b>	229.7 <sup>c</sup>	29.3	30	166
$\text{CH}_3-\text{CH}=\text{N}-\text{H}$	<b>4e</b>	234.7 <sup>c</sup>	34.0	26	157
$(\text{CH}_3)_2-\text{C}=\text{N}-\text{H}$	<b>4f</b>	221	20.6	17	141

<sup>a</sup> Values taken from ref. 8a

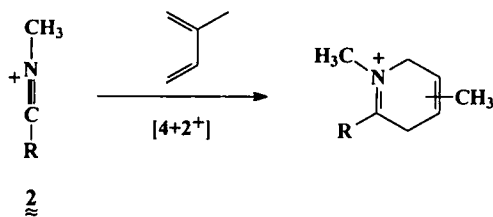
<sup>b</sup> Given as  $\text{PA}(\text{molecule}) - \text{PA}(\text{isoprene})$ . This corresponds to the enthalpy of the proton transfer reaction from  $\text{MH}^+$  to isoprene

<sup>c</sup> Calculated from  $\Delta H_f^\circ$  data in this table using  $\Delta H_f^\circ(\text{H}^+) = 365.7$  kcal/mol

**Nitrilium ions 2** In striking contrast to the behavior of *N*-protonated acetonitrile (i.e., ion **1b**), its isomer (the protonated isonitrile **2a**) reacts readily with isoprene to give the intact adduct (Figure 1b), identified as the [4 + 2<sup>+</sup>] Diels-Alder cycloadduct (Scheme II), as discussed in subsequent text. The proton transfer reaction occurs to only a small extent for ion **2a**. Cycloaddition of **2a** to isoprene is favored over the competing proton transfer reaction by the fact that the latter reaction is mildly endothermic (by 1.0 kcal/mol, Table 2). The cycloaddition reactivity of **2a** is in striking contrast to its isomer **1b**, for which the highly exothermic proton transfer reaction predominates. A similar case is presented by protonated ketene (CH<sub>2</sub>=C=O<sup>+</sup>-H), which reacts extensively with isoprene by proton transfer, whereas its isomer, the acetyl cation CH<sub>3</sub>-C≡O<sup>+</sup>, reacts by proton transfer to a modest degree while the dominant reaction channel is cycloaddition [21b, c]. The proton affinity of the common conjugate base, that is, ketene [8a], is considerably lower at oxygen than carbon, thus favoring the proton transfer reaction for O-protonated ketene over the acetyl ion.

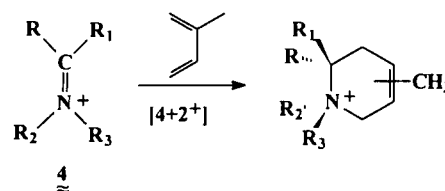
In parallel with the behavior of ion **2a**, its homolog **3** (*m/z* 56; H-C≡N-C<sub>2</sub>H<sub>5</sub><sup>+</sup>) reacts with isoprene to form the corresponding adduct at *m/z* 124 (Table 1), although the extent to which this reaction occurs and also the overall reactivity of the ion are both smaller than for ion **2a**. The cycloaddition reactivity shown by ion **3** stands in contrast to the main proton transfer reaction displayed by its isomer-ion **1c**. Note that proton transfer to isoprene is exothermic for **1c** and endothermic for **3** (Table 2).

A dramatic change in reactivity is observed when the methyne hydrogen in **2a** is replaced by a methyl (**2b**), ethyl (**2c**), or phenyl (**2d**) group, respectively. These nitrilium ions display a very low overall reactivity (Table 1), most of the Q1 mass-selected ion beam survives the ion-molecule reaction conditions in Q2, and the MS<sup>2</sup> reaction product spectra are therefore dominated by the precursor ion. The corresponding cycloadducts are not observed at all, whereas the proton transfer products are displayed only in very low abundance. Ion **2c** shows a little fragmentation by ethene loss under the low-energy collision conditions employed, and is likely to yield ion **2a** at *m/z* 42,



- a** : R = H  
**e** : R = CH<sub>3</sub>CO  
**f** : R = Br

**Scheme II.** [4 + 2<sup>+</sup>] cycloaddition reactions of nitrilium ions with isoprene



**Scheme III.** [4 + 2<sup>+</sup>] cycloaddition reactions of immonium ions with isoprene

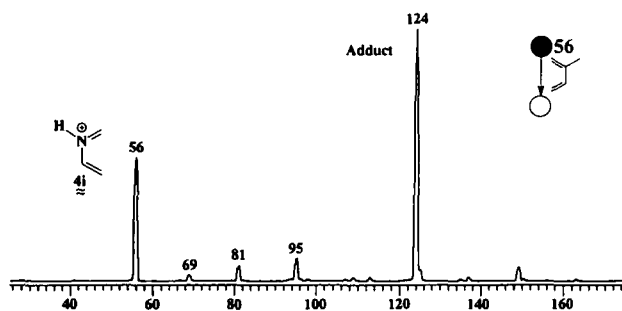
which under the multiple collision conditions reacts further with isoprene to produce the cycloadduct at *m/z* 110. In remarkable contrast to the other C-substituted nitrilium ions **2b-d**, the C-acetyl- (**2e**) and the C-<sup>79</sup>Br- (**2f**) substituted nitrilium ions react well with isoprene to form abundant adducts at *m/z* 152 and 188, respectively (Table 1).

**Immonium ions** In solution, electron-deficient imino dienophiles, especially imino cation salts, have been used successfully in cycloaddition reactions in a number of cases [17]. A systematic series of several immonium ions (**4a-j**) was therefore investigated for their ability to undergo gas-phase [4 + 2<sup>+</sup>] cycloaddition reactions with isoprene. The simplest member of the immonium ion series, that is, ion **4a** (CH<sub>2</sub>=NH<sub>2</sub><sup>+</sup>) reacts extremely well with isoprene to form an abundant adduct at *m/z* 98 (Table 1), identified as the [4 + 2<sup>+</sup>] cycloaddition product (Scheme III), by the arguments discussed in the following text. The proton transfer reaction scarcely occurs for this ion. As also observed for the nitrilium ions, alkyl substitution dramatically decreases the extent to which both the cycloaddition and proton transfer reactions occur. Although the *N*-mono-alkyl-substituted immonium ions **4b** and **4c** show low abundance cycloaddition products, the *N*-dialkyl-substituted immonium ion **4d**, the C-monoalkyl substituted ion **4e**, and the dialkyl substituted **4f** ions are practically unreactive toward isoprene (overall reactivity below 1%).

The *N*-phenyl-substituted ion (**4g**) favors cycloaddition as does *N*-acetyl substitution (**4h**). Both ions readily undergo adduct formation to yield the products ions at *m/z* 174 and 140, respectively (Table 1). Two immonium ions that correspond to the protonated forms of the 2-aza- (**4i**) and 1-aza-butadiene (**4j**) also were studied. Similarly to the ion-molecule chemistry displayed by the other two α,β-unsaturated immonium ions **4g-h**, the 2-aza isomer **4i** reacts readily with isoprene to form a very abundant adduct at *m/z* 124 (Figure 2). The vinyl-substituted ion **4j**, however, is much less reactive with isoprene, and its MS<sup>2</sup> ion-molecule reaction spectrum (Table 1) is dominated by the precursor ion, whereas the adduct (*m/z* 124) is observed in quite modest abundance.

### Theoretical Calculations

Radical cation or even-electron cation dienophiles often are incorporated into synthetic strategies in solu-



**Figure 2.** MS<sup>2</sup> product spectrum for the ion-molecule reaction with isoprene of the mass-selected vinyl-substituted  $\alpha,\beta$ -unsaturated immonium ion **4i**, the N-protonated form of 2-azabutadiene, that shows an abundant cycloaddition product at  $m/z$  124.

tion. The very polar bonds in these electron-deficient dienophiles promote cycloaddition, in the case of radical cations, by "hole-catalyzed" [20] cycloadditions with electron-rich dienes. Although the term "hole-catalyzed" refers to radical cations, certain even-electron dienophiles are also highly activated toward cycloaddition. This is seen in the present work, previous gas-phase studies of the  $\text{CH}_3\text{-C}\equiv\text{O}^+$  ion [21b], several of its homologs [21c] and its sulfur analog, the  $\text{CH}_3\text{-C}\equiv\text{S}^+$  cation [21b], and by solution cycloadditions that employed immonium [17] and oxonium ions [19]. Following this argument, all, not just some, of the nitrilium ions discussed in the foregoing text would be expected to react with isoprene by cycloaddition. To address, at a fundamental level, the dramatic differences in reactivity observed, frontier orbital energies for these ions were calculated by the AM1 method [27] and the results are presented in Table 3 and Figure 3. The underlying assumption used here, based on earlier work on Diels-Alder reactions in solution, is that cycloaddition reactivity correlates with the HOMO-LUMO energy gap [31].

Among the two possible HOMO-LUMO combinations, the AM1 energies indicate, as expected, that the LUMO(ion) and HOMO(isoprene) should be the frontier orbitals used to predict the trends in cycloaddition reactivity. As shown, the LUMO(ion) - HOMO(isoprene) energy difference is 3.79 kcal/mol or less for **2a** and **3**, the alkyl-substituted ions that form cycloadducts. Although relatively small HOMO-LUMO gaps also are noted for the N-protonated nitriles, that is, the nitrilium ions **1** (Table 3), their lack of cycloaddition is reconciled by noting that these ions react mainly by the competitive exothermic (Table 2) proton transfer route. The C-alkyl substituted ions **2b-d** display the largest energy gaps (Figure 3 and Table 3) and this therefore appears as the dominant factor that suppresses cycloaddition. The higher proton affinities of the conjugated bases also could explain their very low overall reactivities. On the other hand, the electron-withdrawing acetyl and bromine groups of ions **2e** and **2f** lower the LUMO energies considerably (Figure 3, Table 3), which leads to small LUMO-HOMO gaps

**Table 3.** HOMO and LUMO energies and enthalpy of formation of ionic products

	HOMO (eV)	LUMO (eV)	Gap <sup>a</sup> (eV)	Cyclo-addition	$\Delta H_f$ (kcal/mol)
<b>Isoprene</b>	-9.21	0.50			23.2
<b>1a</b>	-21.95	-6.11	3.10	No	214.8
<b>1b</b>	-18.84	-5.62	3.59	No	196.1
<b>1c</b>	-16.96	-5.46	3.75	No	188.3
<b>1d</b>	-14.13	-5.55	3.66	No	224.2
<b>2a</b>	-18.37	-5.60	3.61	Yes	208.1
<b>2b</b>	-17.45	-5.20	4.01	No	190.6
<b>2c</b>	-16.56	-5.07	4.14	No	183.1
<b>2d</b>	-13.88	-5.25	3.96	No	219.9
<b>2e</b>	-16.93	-5.93	3.28	Yes	173.7
<b>2f</b>	-17.03	-6.42	2.79	Yes	213.1
<b>3</b>	-16.70	-5.42	3.79	Yes	201.4
<b>4a</b>	-19.87	-6.52	2.70	Yes	176.3
<b>4b</b>	-17.75	-6.14	3.07	Yes <sup>b</sup>	174.1
<b>4c</b>	-16.70	-5.99	3.22	Yes <sup>b</sup>	151.4
<b>4d</b>	-17.13	-5.84	3.37	No	174.7
<b>4e</b>	-18.13	-6.14	3.07	Yes <sup>b</sup>	159.7
<b>4f</b>	-17.78	-5.88	3.33	No	147.6
<b>4g</b>	-13.90	-5.86	3.35	Yes	202.8
<b>4h</b>	-17.13	-6.44	2.77	Yes	146.1
<b>4i</b>	-15.53	-6.22	2.99	Yes	196.8
<b>4j</b>	-15.82	-6.20	3.01	Yes <sup>b</sup>	180.6
<b>CH<sub>3</sub>C≡S<sup>+</sup></b>	-17.67	-6.86	2.35	Yes <sup>c</sup>	196.1
<b>CH<sub>3</sub>≡O<sup>+</sup></b>	-20.17	-6.98	2.23	Yes <sup>c</sup>	164.5

<sup>a</sup> Gap =  $E_{\text{LUMO(ion)}} - E_{\text{HOMO(isoprene)}}$

<sup>b</sup> The cycloadduct is observed but in low abundance

<sup>c</sup>  $\text{CH}_3\text{C}\equiv\text{O}^+$  and  $\text{CH}_3\text{C}\equiv\text{S}^+$  cycloaddition was taken from ref 21a, b

and favors cycloaddition. In addition, the high cycloaddition reactivity of **2e** and **2f**, despite the presence of bulky substituents, apparently rules out severe reaction-limiting steric effects for the cycloaddition process. It is interesting to note that small LUMO-HOMO gaps (Table 3) also can be invoked, together with the low proton affinity of their conjugate bases, to explain the high cycloaddition reactivity of the  $\text{CH}_3\text{-C}\equiv\text{O}^+$  and  $\text{CH}_3\text{-C}\equiv\text{S}^+$  ions [21b, c].

The results for ions **4a-f** show that cycloaddition reactivity also can be explained by the HOMO-LUMO energy gap (Table 3). They also indicate that alkyl substituents on carbon decrease the reactivity of the ions by raising the LUMO energy more than does substitution at nitrogen, as experimentally observed (Table 1). Ion **4g** shows a high cycloaddition reactivity despite the fact that its LUMO energy is rather high within the homologous series. This could be an effect of product stabilization provided by charge delocalization on the phenyl ring. Ions **4h** and **4i** display relatively low LUMO energies, which is in accordance with their high cycloaddition reactivity. The LUMO-HOMO energy gap fails, however, to predict the reactivity of ion **4j**. This ion should demonstrate good cycloaddition reactivity with isoprene based on its LUMO energy, as is the case for ion **4i** (Table 3), but low reactivity is observed (Table 1). All these gas-phase results on the effects of HOMO-LUMO gaps correspond to solution reactions where the control of gap energy has long been known [31].

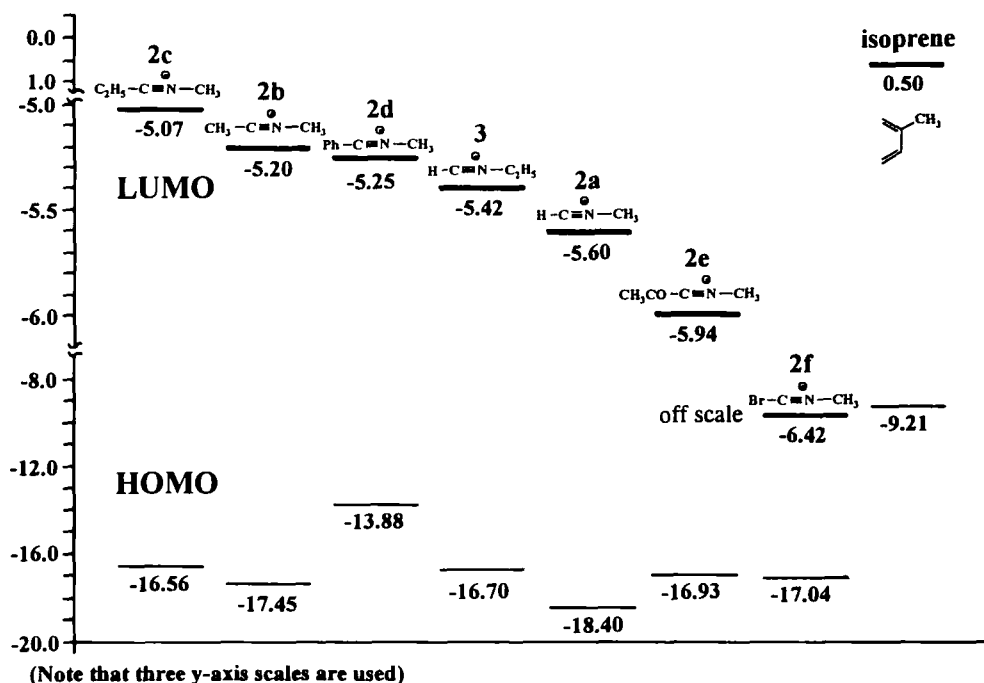
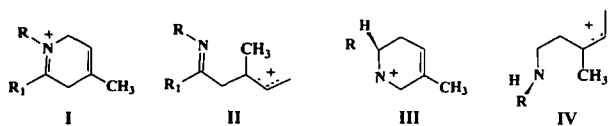


Figure 3. Highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbital energy diagram for the reactions of isoprene with the nitrilium ions 2 and 3.

*Cyclic versus open-ring adducts.* There exist two alternative pathways by which covalently bound adducts could be produced from reactions between the nitrilium and immonium ions with isoprene. One would involve a simple addition mechanism in which the open-ring adducts II or IV would be produced (Scheme IV). A [4 + 2<sup>+</sup>] cycloaddition mechanism would lead to the cyclic ions I or III (Scheme IV). The AM1 calculations on several isomeric pairs show that in all cases, the cyclic ions are the most thermodynamically favorable products (Table 4). Note that only the results for the most stable product that results from simple addition to isoprene (attack at the C<sub>1</sub> carbon) are presented in Table 4.

### MS<sup>3</sup> Experiments

To obtain experimental information on the structures of the adducts formed with isoprene, MS<sup>3</sup> sequential product scans [16] were utilized. The adducts formed



a, R=CH<sub>3</sub>, R<sub>1</sub>=H

b, R=Et, R<sub>1</sub>=H

c, R=CH<sub>3</sub>, R<sub>1</sub>=CH<sub>3</sub>CO

a, R=H

b, R=CH<sub>3</sub>CO

c, R=Ph

Scheme IV. The structures of cyclic and open-ring product ions.

in Q2 from the reaction of Q1 mass-selected ions with isoprene were mass-selected by using Q3 and dissociated in Q4 by using 10-eV collisions with argon.

*Nitrilium ions.* The MS<sup>3</sup> spectrum (Figure 4a) of the adduct at *m/z* 110 formed in reactions with ion 2a (Figure 1b) fragments to yield (i) *m/z* 69, assigned as protonated isoprene, (ii) *m/z* 42 (C<sub>2</sub>H<sub>4</sub>N<sup>+</sup>), attributed to the retro-Diels-Alder fragment ion, and (iii) a low abundance ion of *m/z* 41, assigned as C<sub>3</sub>H<sub>5</sub><sup>+</sup>. These assignments were confirmed by reacting isoprene with the *d*<sub>3</sub>-isomer 2a' (HC≡N—CD<sub>3</sub><sup>+</sup>; *m/z* 45) formed by CD<sub>3</sub>I chemical ionization of HCN. When the deuterated adduct (*m/z* 113) was dissociated in a sequential product scan [16], the product ions at *m/z* 41 and 69 did not shift in mass, whereas *m/z* 42 shifted to *m/z* 45. Confirmation of the origin of *m/z* 41 as a fragment of *m/z* 69 was obtained by mass-selection and dissociation of the protonated isoprene. The primary fragment was *m/z* 41 [100% relative abundance (RA)],

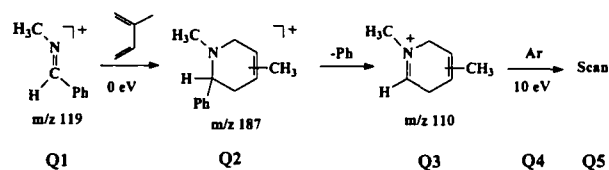
Table 4. AM1 calculations of heats of formation of several cyclic and open-ring adducts (kcal/mol)

	I	II	ΔE
a	170.1	212.2	42.1
b	162.7	206.5	43.8
c	141.3	178.1	36.8
	III	IV	ΔE
a	149.9	185.8	35.9
b	129.5	145.4	15.9
c	187.6	216.8	29.2

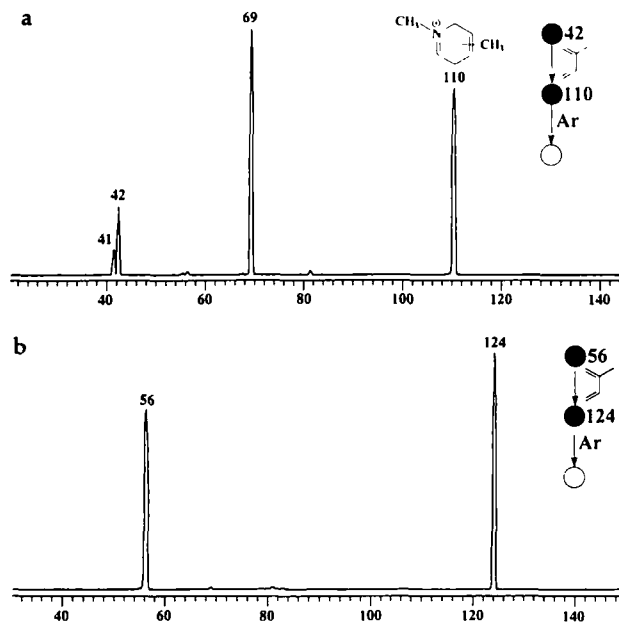
with smaller amounts of  $m/z$  39 (4.8% RA) and  $m/z$  53 (1.6% RA) observed. The mass-selected adduct from the reaction of isoprene with **3** ( $\text{HC}\equiv\text{N}^+ - \text{C}_2\text{H}_5$ ) dissociates in a similar manner as revealed in a  $\text{MS}^3$  sequential product scan. This spectrum displays fragment ions that correspond to protonated isoprene ( $m/z$  69; 78% RA), the precursor ion ( $m/z$  56; 18% RA), and a small amount of  $m/z$  41 (2% RA). This fragmentation behavior also proves the covalently bound nature of the adduct, and rules out any loosely bound structure, including the proton bound dimer. Such a dimeric ion should fragment mainly to give the protonated form of the higher proton affinity constituent [32], that is, it is expected to yield the original reactant ion, not protonated isoprene (Table 2). The  $\text{MS}^3$  spectrum of the adduct  $m/z$  147 from reaction of **2f** with isoprene also shows a similar fragmentation pattern and most likely loses neutral isonitrile to yield the  $\text{Br-isoprene}^+$  ion.

The acetyl group affects the dissociation chemistry of the isoprene adduct of **2e** considerably, as revealed by the  $\text{MS}^3$  experiment. The CID fragmentations are dominated by a series of structurally characteristic neutral losses and these are interpreted as follows.  $m/z$  110 [82%, loss of ketene ( $\text{CH}_2=\text{C}=\text{O}$ )],  $m/z$  109 (100%, loss of  $\text{CH}_3-\text{N}=\text{CH}_2$  or the acetyl radical),  $m/z$  84 (27%, loss of isoprene, i.e., the retro-Diels-Alder ionic product),  $m/z$  43 [79%, loss of  $\text{C}_7\text{H}_{11}\text{N}$  to form the acetyl cation ( $\text{CH}_3-\text{C}\equiv\text{O}^+$ )], and  $m/z$  42 (25%, loss of isoprene, i.e., the retro-Diels-Alder product of  $m/z$  110).

An attempt also was made to generate the authentic adduct of **2a** at  $m/z$  110 and to record its  $\text{MS}^3$  sequential product spectrum. This was accomplished by mass-selecting the molecular ion of *N*-benzylidenemethylamine by using Q1 (Scheme V) and by forming an adduct with isoprene in Q2. Dissociation by phenyl loss yields an ion  $m/z$  110, which is a candidate for the structure of the isoprene adduct of the nitrilium ion **2a**. This ion was then mass-selected by using Q3 and dissociated in Q4. Fragmentation yielded  $m/z$  42 and 69, both of which also occur in the isoprene adduct of ion **2a** (Figure 4a). However, the *N*-benzylidenemethylamine-derived ion also fragments by  $\text{H}_2$  loss. This result suggests that a mixture of  $m/z$  110 structures is formed, one of which appears to be the isoprene cycloadduct of **2a**.



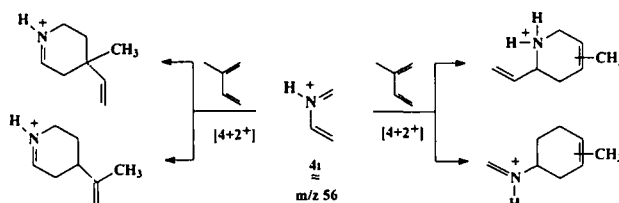
**Scheme V.** Mechanistic study of the  $[4 + 2^+]$  reaction of immonium ion with isoprene by using the *N*-benzylidenemethylamine radical cation as the authentic precursor ion.



**Figure 4.**  $\text{MS}^3$  sequential product spectrum of the  $[4 + 2^+]$  cycloadduct formed in reactions of (a) ion **2a** and (b) ion **4i** with isoprene that shows (a) the retro-Diels-Alder CID product at  $m/z$  42, protonated isoprene at  $m/z$  69, and its loss of  $\text{C}_2\text{H}_4$  fragment at  $m/z$  41 and (b) only the retro-Diels-Alder product at  $m/z$  56

**Immonium ions.** The  $\text{MS}^3$  spectra for the adducts generated by reaction of the immonium ions **4a**, **4g**, **4h**, and **4i** with isoprene all display a single identical fragmentation pathway that is assigned to the retro-Diels-Alder fragmentation process, because it is also the case for the cycloadducts of the acylium ions [21b, c]. The sequential product spectrum for **4i** is shown in Figure 4b. The lack of any other fragments in Figure 4b does not permit one to distinguish among the four possible structures for this specific cycloadduct, which include two  $[4^+ + 2]$  and two  $[4 + 2^+]$  alternatives (Scheme VI).

To further establish the nature of the cycloaddition product, two independent experiments were performed and their results were compared. The immonium ion **4a** was reacted with butadiene and the  $\text{MS}^3$  spectrum of the adduct at  $m/z$  84 was compared to the CID  $\text{MS}^2$  spectrum of protonated 1,2,3,6-tetrahydropyridine—the authentic cyclic ion obtained from chemical ionization of 1,2,3,6-tetrahydropyridine with methane. Similar fragmentation behavior ( $m/z$  30 as



**Scheme VI.** Possible cycloaddition pathways for reaction of protonated 2-aza-butadiene (**4i**) with isoprene



the only fragment) was obtained (spectra not shown) that strongly indicates that the immonium ion **4a** reacts with isoprene to yield the cyclic product, as is also supported by the theoretical calculations already discussed.

### Isomer Distinction

Although emphasis has not been given to isomer distinction in this study, it is clear that these reactions can be useful in the identification of the ions investigated from isomeric alternatives. For instance, it is interesting to note the very distinctive chemical behavior of the five isomeric C<sub>3</sub>H<sub>6</sub>N<sup>+</sup> (*m/z* 56) cations.

**1c** (C<sub>2</sub>H<sub>5</sub>-C≡N<sup>+</sup>-H),

**2b** (CH<sub>3</sub>-C≡N<sup>+</sup>-CH<sub>3</sub>),

**3** (H-C≡N<sup>+</sup>-C<sub>2</sub>H<sub>5</sub>),

**4i** (CH<sub>2</sub>=N<sup>+</sup>H-CH=CH<sub>2</sub>), and

**4j** (<sup>+</sup>NH<sub>2</sub>=CH-CH=CH<sub>2</sub>) Ion **1c** reacts extensively with isoprene by proton transfer (Figure 1a); no adduct is observed. Ions **2b** and **4j** are quite unreactive (Table 1), but only **4j** shows adduct formation. Ions **3** (Table 1) and **4i** (Figure 2) react extensively with isoprene to form abundant cycloadducts. Their distinction is, however, still possible when MS<sup>3</sup> experiments are employed, because the two adducts display distinctive CID behavior (see text and Figure 4b).

### Conclusions

The gas-phase reactions of nitrilium and immonium ions with isoprene have been examined and it was found that these ions react by cycloaddition and/or proton transfer. The reactivity and mechanism of the reactions are dependent on the nitrilium and immonium ions studied, and are influenced primarily by the LUMO molecular orbital energies of the ions. The substituents on the ion, the proton affinity of its conjugate base, and the thermochemistry of the proton transfer reaction all affect reactivity and are rationalized. Adduct formation can be predicted by knowing the LUMO(ion)-HOMO(isoprene) energy difference and taking into account the possibility of competing exothermic proton transfer reactions. When the LUMO(ion)-HOMO(isoprene) energy gap is small and the proton affinity of the conjugate Bronsted base is greater than that of isoprene, that is, for those ions (**2a**, **2e**, **2f**, **3**, **4a**, **4g**, **4h**, and **4i**) with the most negative LUMO energies, the predicted occurrence of cycloaddition to isoprene has been confirmed by experiment. Nitrilium ions with R-C≡N<sup>+</sup>-H structures (**1a-d**) react mainly by proton transfer, as dictated by the low proton affinity of their conjugate bases.

The MS<sup>3</sup> experiments provide important structural information on the ionic products, which shows these products to be covalently bound and gives evidence for the [4 + 2<sup>+</sup>] cycloadduct structures, which also are supported by the AM1 calculations.

Considering the importance of nitrilium and immonium ions both in the gas phase and in solution, their ion-molecule chemistry elucidated in this study should be useful. A case in point is isomer distinction, as clearly shown for the five C<sub>3</sub>H<sub>6</sub>N<sup>+</sup> (*m/z* 56) isomers. The findings should also have value for trapping strategies or in comparisons between solution versus gas-phase chemical behavior that can lead to evaluations of solvent effects.

### Acknowledgments

This work was supported by the National Science Foundation (CHE 92-2371) MNE acknowledges support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Brazil

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