Polar [4 + 2⁺] Diels–Alder Cycloadditions of Acylium Ions in the Gas Phase

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Abstract: Acylium ions react with neutral isoprene and other 1,3-dienes in the gas phase to form covalently bound adducts by polar [4 + 2⁺] Diels–Alder cycloaddition. This general reaction was previously unknown either in the gas phase or as the corresponding solution reaction, but the mechanism is supported by *ab initio* calculations and experimental studies. Proton transfer competes with cycloaddition, as does fragmentation of both the acylium ion and the nascent cycloaddition product. Structural information on the ion/molecule product is obtained by performing multiple-stage (MS^3) experiments using a pentaquadrupole mass spectrometer. Cycloreversion dominates the fragmentation behavior of these adducts. Both alkyl- and aryl-substituted acylium ions, as well as the thioacetyl cation, undergo facile cycloaddition. The α,β-unsaturated acylium ions (**13** and **17**) undergo a novel cycloaddition reaction at the double bond, the positively charged $C{\equiv}O^+$ acting as an activating group. Substitution at the C=C double bond (**14–16**) can change the regioselectivity redirecting cycloaddition to the $C{\equiv}O^+$ bond, as shown by MS^3 experiments which display cycloreversion only when addition is on the carbonyl.

Introduction

The overwhelming importance of Diels–Alder cycloaddition reactions in organic chemistry is well-known and thoroughly documented.[1] Many synthetic routes to important cyclic compounds are made possible through these [4 + 2] cycloaddition reactions, which can involve a large variety of dienes and dienophiles. Although Diels–Alder reactions usually employ uncharged or dipolar components, many positively and negatively charged species generated in solution are also used as reagents in reactions known as polar Diels–Alder cycloadditions.[1,2] Even-electron cations sometimes show greatly improved yields over those for the corresponding nonpolar Diels–Alder cycloadditions, as demonstrated in the reactions involving alkoxy-substituted allyl cations prepared from the acetals of acrolein.[3] The improved yields of the C=C cycloaddition products are due to activation by the strongly electron withdrawing, positively-charged substituent. Reactions with radical cations, which can be prepared in solutions of inert solvents, were recently incorporated into the category of polar Diels–Alder cycloadditions. These reactions have been used in various efficient ("hole catalyzed") synthetic routes and show some advantages with respect to neutral cycloadditions.[4] Several carbocycles and heterocycles have been synthesized from ionic components by application of this new reaction principle.

The mass spectrometer provides a convenient environment in which to study the chemical behavior of ionic species and to seek parallels with solution chemistry. This is especially so since multidimensional mass spectrometric experiments, such as MS/MS and MS^3, allow reactions to be performed with mass-selected reagent ions as well as allow the (mass) selected products of ion/molecule reactions to be structurally characterized.[5] An advantageous feature of such an approach is that a large variety of ions can be generated easily in the gas phase by ionization and/or fragmentation of appropriate compounds and also by ion/molecule reactions. Polar cycloaddition reactions of radical cations have been investigated in the gas phase,[6] and they often reveal greater reactivity than that observed for the corresponding neutral reactions in solution. For example, vinyl methyl ether radical cations react efficiently with 1,3-butadiene to form the 4-methoxycyclohexene radical cation.[6] The corresponding reaction involving the two neutral compounds has not been reported in solution. Other examples include the [4 + 2] cycloaddition of ionized styrene with neutral styrene, yielding ionized phenyltetralin,[6c] and the [2 + 2] and [4 + 2] cycloadditions of the molecular ion of cyclobutadiene, with several neutral reagents.[5c] On the other hand, ionized alkenes undergo simple addition to neutral alkenes.[6g] Very little attention, however, has been devoted to gas-phase cycloaddition reactions involving even-electron cations, which is the subject of the present study. Nibbering and co-workers[7a] studied allyl cation addition to vinyl methyl ether and found evidence for [2 + 3⁺] cycloaddition as well as simple addition. Keough[7b] studied the $(M-H)^+$ oxonium ion generated when using dimethyl ether as a chemical ionization

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reagent gas and found evidence, based on the formation or nonformation of a stable adduct, for cycloaddition in those cases where the dienes undergo Diels–Alder reactions in solution. An ion trap investigation from this laboratory[7c] using MS^3 experiments has provided evidence that the $(M - H)^+$ ion of pyrene undergoes [4 + 2⁺] cycloaddition with isoprene. In all these cases, the evidence for cycloaddition to closed-shell ions is rather limited.

Acylium ions are among the most stable, most accessible, and best-characterized classes of carbocations in solution chemistry.[8] Their importance is exemplified by their participation in the Friedel–Crafts acylation reaction and other important processes.[9] These even-electron cations can be generated readily in the gas phase in several ways, such as by α-cleavage fragmentation of ionized carbonyl compounds, or from other oxygenated compounds by more complex fragmentation mechanisms[5b,10] or by ion/molecule reactions.[11] Acylium ions are stable gas-phase species and are not expected to undergo interconversion to isomeric structures, since theoretical calculations on model ions show them to exist in deep potential wells and to be more stable than their structural isomers.[12]

The ion/molecule chemistry of some acylium ions, mainly the acetyl cation, has been explored by several techniques.[11,13] In analogy to solution-phase reactions, acylation involving the acetyl cation is the most studied reaction. Other reactions of this ion include oxygen displacement by sulfur,[11b] methylation,[13d] and bromine displacement.[13c] Recent results from our laboratory on the acetyl cation[5b] suggest that acylium ions in general should display a rich gas-phase reactivity, which includes cycloaddition chemistry. We observed[5b] the acetyl cation to react with isoprene in a reaction not shared by its two most stable isomers, O-protonated ketene and the oxiranyl cation. The reaction led to formation of an abundant adduct and was ascribed to a polar [4 + 2⁺] Diels–Alder cycloaddition.[14] This reaction of the acetyl cation is without precedent in either the gas or solution phase, and the present study therefore investigates in detail the gas-phase cycloaddition reactivity of a variety of acylium ions. Evidence for [4 + 2⁺] cycloaddition and information on regioselectivity was obtained through product characterization by performing MS^3 experiments in a pentaquadrupole mass spectrometer.[16] Ab initio molecular orbital calculations were employed to study the energetics of the competitive reaction pathways.

Experimental Section

The MS^2 and MS^3 experiments were performed using a pentaquadrupole mass spectrometer[16] consisting of three mass-analyzing quadrupoles (Q1, Q3, Q5) and two reaction quadrupoles (Q2, Q4). For the MS^2 experiments, the ion to be studied was generated by 70-eV electron ionization (EI) and mass-selected using Q1. After undergoing an ion/molecule reaction in Q2 with the neutral reagent of choice, Q3 was used to record the product spectrum, while Q5 was operated in the nonanalyzing RF-only mode. Nominal sample and neutral gas pressures were typically 5×10^{-6} and 5×10^{-5} Torr, respectively, as monitored by a single ionization gauge located centrally in the vacuum chamber. The target gas pressure corresponds to a typical beam attenuation of 50%, viz., to multiple collision conditions. Instrument parameters such as quadrupole offset potentials and lens voltages were adjusted to maximize the abundance of the ion/molecule products.

For the MS^3 experiments, ion/molecule reactions with a neutral gas were performed in Q2 and collision-induced dissociation (CID) with argon was performed in Q4. The ions of interest generated in the ion source were again selected using Q1, and an ion/molecule reaction product was selected in Q3, while Q5 was scanned to record the sequential product MS^3 spectrum. The collision energy, calculated as the voltage difference between the ion source (grounded) and the collision quadrupole, was typically near 0 eV for ion/molecule reactions and 10 eV for CID, in both MS^2 and MS^3 experiments.

The ions of interest were generated from the following precursor molecules: **1** (acetaldehyde), **2** (acetylacetone),[5b] **3** (3-pentanone), **4** (3-octanone), **5** (methyl phenyl ketone), **6** (*p*-methoxyphenyl methyl ketone), **7** (methyl *p*-nitrophenyl ketone), **8** (*N*-methylacetamide), **9** (*N*,*N*-dimethylformamide), **10** (acetic acid), **11** (methyl acetate), **12** (acetyl chloride), **13**, **14**, **15**, and **16** (2-methylcyclohexanone), **17** [(*R*)-(+)-α-methylbenzyl isocyanate], and **18** (thioacetamide).[17] All compounds except 3-methylenecyclohexene were commercially available and used without further purification. 3-Methylenecyclohexene was prepared from the corresponding ketone by the Wittig reaction, isolated by distillation, and characterized by ^{13}C NMR and ^1H NMR spectroscopy.

Molecular orbital calculations were performed using the GAMESS[18] program. Structure optimizations using gradient techniques were performed at the Hartree–Fock (HF) level of theory using the 6-31G** basis set. Improved energies were obtained by using single-point calculations at the 6-31G** level, including valence electron correlations calculated by second-order Møller–Plesset perturbation theory. These latter calculations are denoted as MP2/6-31G**//6-31G**.

Results and Discussion

Product ion spectra, that is, mass spectra which record the products of ion/molecule reactions of mass-selected reagent ions with isoprene, are reported in Table I. Additional results for other neutral reagents are incorporated into the body of the Results and Discussion. The spectra for the acylium ions **1**–**18** show three competitive reaction channels: (i) adduct formation, shown to be due to cycloaddition, (ii) proton transfer, and (iii) fragmentation. The nature of the substituents is observed to control the relative importance of these processes, as discussed below. The acetyl cation (**2**) has previously been demonstrated[5b] to react with isoprene by [4 + 2⁺] cycloaddition at the C≡O⁺ bond, forming *m*/*z* 111 (Scheme I).[19] The regioselectivity is not known, and the evidence for cycloaddition is presented in the next section.

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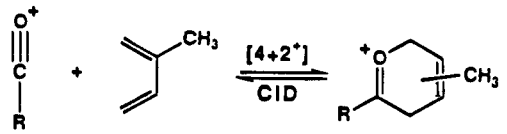
(19) Only the ortho cycloadduct is shown in the schemes, although the alternative regioselectivity is not excluded.

Table I. MS^2 Product Spectral Data[a] for Ion/Molecule Reactions with Isoprene

ion		m/z	product m/z (relative abundance)[b]: cycloadducts and/or their fragments	proton-transfer[a] and/or charge-exchange products	cycloadduct[c]: m/z 81 ratio	fragments of the reagent ion or products
1	$HC{\equiv}O^+$	29		81 (100)		
2[d]	$H_3CC{\equiv}O^+$	43	111 (100)	81 (10)	10	
3[e]	$H_5C_2C{\equiv}O^+$	57	125 (100)	81 (27)	3.7	29 (5)
4[e]	$n\text{-}H_{11}C_5C{\equiv}O^+$	99	167 (73)	81 (70)	1.4	71 (100), 43 (25)
5	$PhC{\equiv}O^+$	105	173 (100)	81 (6)	17	77 (29)
6	$p\text{-}H_3COC_6H_4C{\equiv}O^+$	135	203 (100)	81 (26)	3.8	107 (5), 92 (15), 77 (7)[f]
7	$p\text{-}O_2NC_6H_4C{\equiv}O^+$	150	218 (100)	68 (10), 81 (28)	3.6	120 (14), 104 (50), 92 (51), 76 (4)[g]
8	$H_3CNHC{\equiv}O^+$	58		81 (100)		
9	$(H_3C)_2NC{\equiv}O^+$	72	140 (100)	81 (6)	17	44 (6)
10	$HOC{\equiv}O^+$	45		81 (100)		
11	$H_3COC{\equiv}O^+$	59	127 (53), 85 (18)	81 (100)	0.7	
12	$ClC{\equiv}O^+$	63		81 (100), 68 (32)		
13[e]	$H_2C{=}CHC{\equiv}O^+$	55	123 (5), 95 (100)	81 (15)	7	
14[e]	$H_2C{=}C(CH_3)C{\equiv}O^+$	69	137 (100), 109 (85)	81 (43)	4.3	41 (2)
15	$H_3CHC{=}C(CH_3)C{\equiv}O^+$	83	151 (100), 123 (22)	81 (23)	5.3	55 (5)
16	$H_2C{=}C(i\text{-}C_3H_7)C{\equiv}O^+$	97	165 (100), 147 (11)	81 (9)	12.3	69 (8)[h]
17	$PhHC{=}NC{\equiv}O^+$	132	200 (100), 157 (10), 105 (43)	81 (5)	22	173 (13), 77 (10)
18[d]	$H_3CC{\equiv}S^+$	59	127 (100)	81 (29)	3.4	

[a] The reagent ion and proton-transfer products other than m/z 81 are not reported; see text. [b] Relative to the major peak, excluding the reagent ion. [c] The sum of the relative abundance of the cycloadduct and/or its fragments. [d] Data from ref 5b. [e] Complete spectrum shown as a figure; see text. [f] Some unassigned ions observed are 121 (13), 128 (7), 129 (12), 132 (6), and 160 (3). [g] Some unassigned ions observed are 91 (5), 117 (9), and 160 (8). [h] A mixture of a reagent ion fragment and protonated isoprene.

Scheme I



Besides cycloaddition, the acetyl ion reacts by proton transfer to give protonated isoprene, m/z 69. The subsequent ion/molecule reactions of protonated isoprene with neutral isoprene yield a variety of secondary products, the ion m/z 81 being the most abundant.[20] Cycloaddition of the acetyl cation occurs to a much greater extent than proton transfer, the m/z 43 ion formed from acetylacetone reacting with isoprene to yield the two products m/z 111:m/z 81 in an abundance ratio of 10:1. In Table I, only the relative abundance of m/z 81 is reported, the secondary products of the proton-transfer channel being omitted since the same set of ions[20] is observed throughout these experiments and there is little variation in their relative abundances.

Evidence for Diels–Alder [4 + 2⁺] Cycloaddition. Several items of information provide evidence that the ion/molecule reactions of interest proceed via the proposed [4 + 2⁺] cycloaddition mechanism. For convenience they are summarized here, although many points are referred to in more detail later in the paper.

The formation of stable adducts occurs for the acetyl ion but not for its $C_2H_3O^+$ isomers.[5b] The fact that isomeric ions do not yield adducts suggests that simple ion/molecule complexes are not involved. Further evidence against this possibility is provided by comparing the ease with which the adduct dissociates (Table II) with the ease of dissociation of a strongly bound complex, a proton-bound dimer. Proton-bound dimers have strong hydrogen bonds,[21] and numerous studies have shown that they dissociate much more readily than do covalently bound ions.[22] A direct comparison, under the same experimental conditions, was therefore made of the extent of dissociation of the adduct of **2** with isoprene and the proton-bound dimer of acetone. Conditions which yielded a 30:1 ratio of adduct to its major fragment (the reversion product) gave a 1:12 conversion of the proton-bound dimer to the monomer. The adduct is therefore much more strongly bound than the proton-bound dimer, and the difference in dissociation efficiency of more than 2 orders of magnitude leads to the conclusion that it must be covalently bound.

Possible covalent structures include [2 + 2⁺] and [4 + 2⁺] cycloadducts, as well as products of simple acylation. To investigate the last of these possibilities, the reaction of **2** with a conjugated diene, 1,3-butadiene, was compared to its reaction with the nonconjugated diene, limonene, under identical conditions. The former yielded an intact adduct, m/z 97, which had an abundance of 50% of the reactant ion and 78% of the total

Table II. MS^3 Sequential Product Spectral Data of Some Ion/Molecule Reaction Products[a]

reagent ion	product m/z	fragments of the ion/molecule reaction product, m/z (relative abundance)[b]
2[c]	111	93 (0.2), 83 (0.4), 69 (0.3), 55 (0.3), 43 (100)
2[d]	97	43 (100)
2[e]	149	43 (70), 107 (30)
3	125	57 (100), 29 (3)
4	167	99 (100), 71 (20), 69 (4), 43 (26)
5	173	131 (18), 105 (100)
6	203	135 (100), 107 (2), 92 (2), 77 (2)
7	218	150 (100), 120 (3), 104 (8), 92 (4), 76 (2)
9	140	112 (3), 81 (14), 72 (100), 55 (2), 44 (4)
14	137	109 (3), 95 (6), 81 (4) 69 (100), 67 (3)
	109	81 (14), 79 (3), 67 (100), 65 (6), 55 (6), 43 (4), 41 (2)
15	151	83 (100), 69 (25)
	123	95 (5), 81 (100), 67 (10)
16	165	147 (2), 97 (100), 69 (14)
17	157	142 (28), 129 (100), 128 (17), 117 (6), 115 (13), 91 (58), 79 (31), 77 (5)
18[c]	127	99 (36), 93 (100), 91 (18), 79 (3), 77 (22), 65 (4), 59 (27)

[a] Neutral reagent is isoprene unless otherwise indicated. [b] Cycloreversion product is underlined; abundances are relative to the major peak, excluding the selected ion. [c] Data from ref 5b. [d] Neutral reagent is 1,3-butadiene. [e] Neutral reagent is 6,6-dimethylfulvene.

(20) The same set of product ions, with similar relative abundances, is observed for the ion/molecule reaction of $C_3H_7^+$ (or any of a number of other protonating ions) with isoprene, i.e. m/z (relative abundance) 41 (8), 55 (13), 67 (11), 69 (54), 81 (100), 95 (30), 135 (5), 137 (10), 149 (12).

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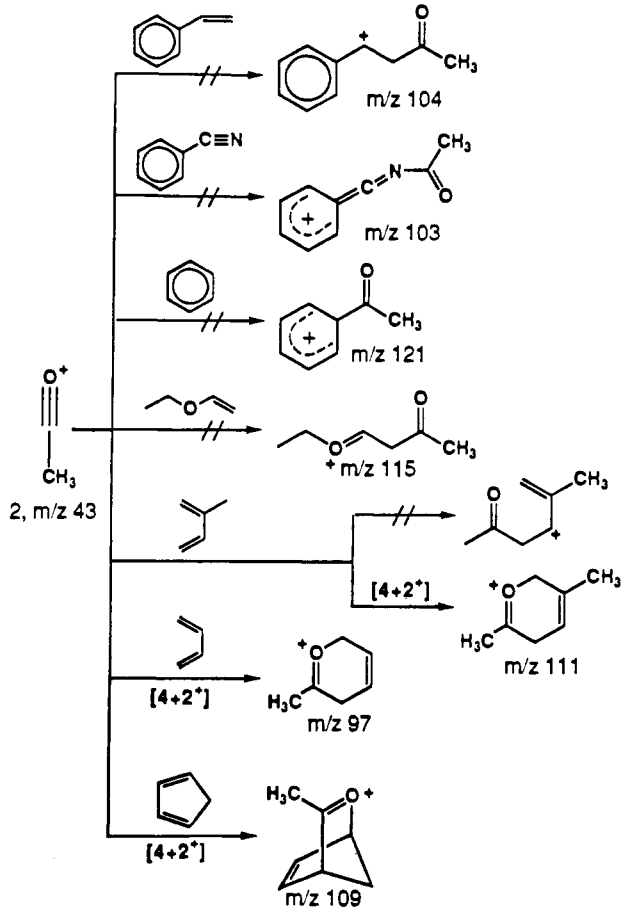
Scheme II



product ion abundance. The latter yielded an adduct of less than 1% of the reactant ion abundance. In an attempt to increase the reactivity of the neutral compound to electrophilic attack, styrene was used as the neutral reagent. Even though the benzylic product shown in Scheme II could have been formed, the adduct was barely detectable (Table III). Similarly, the acetyl cation (**2**) fails to show substantial adduct formation with reagents such as benzene, benzonitrile, and ethyl vinyl ether (Table III), for which product ions with comparable or even greater stability than that formed with butadiene and isoprene would be formed if acylation occurred (Scheme II). Further evidence for cycloaddition is found in the fact that abundant adducts are observed in the product spectra arising from ion/molecule reactions of **2** and the dienes isoprene, 1,3-butadiene, and cyclopentadiene (Table III). Reactions of 6,6-dimethylfulvene also form an adduct with acylium ions,[23] although in this case the predominant process is the competitive protonation of the neutral reagent. When 3-methylenecyclohexene, a diene which is locked in the trans configuration, is used, the adduct is not generated and the product spectrum is dominated by proton transfer. In view of the fact that proton transfer is no more favored in this than many of the other cases examined, the failure to undergo adduct formation is evidence for the requirement of a cis diene.

In light of these results, only cycloaddition remains as a possibility, and [2 + 2⁺] cycloadditions are discounted because [2 + 2⁺] adducts and/or their fragments were not observed, or were observed only in very low relative abundance. This is the case for the reactions between the acetyl cation (**2**) and styrene and ethyl vinyl ether (Scheme II and Table III) and in other similar reactions described in the literature.[11b,24] The foregoing arguments eliminate alternatives to the [4 + 2⁺] cycloaddition mechanism, although they do not prove this mechanism. However, additional evidence for the formation of the cyclic and bicyclic [4 + 2⁺] C≡O⁺ adducts at *m/z* 97, 111, and 109 (Scheme II) is found in their MS³ spectra (Table II). The MS³ sequential product spectra of the cycloadducts *m/z* 97 and 109, formed in the reactions of the acetyl ion with 1,3-butadiene and cyclopentadiene, respectively, show fragmentation to yield *m/z* 43 as the only observable product, while that of the isoprene adduct shows an ion due to loss of 42 (C_3H_6) as an additional but minor process. These results show that the adducts fragment overwhelmingly by the expected retro Diels–Alder process. To confirm this expectation in an independent case, the 3,4-dihydropyrylium ion was prepared by chemical ionization of 3-ethoxy-3,4-dihydro-2*H*-pyran, and its ethanol loss fragment, *m/z* 83, was examined by collision-induced dissociation. Only two products, *m/z* 57 (10% relative abundance) and *m/z* 29 (1% relative abundance), were observed. They correspond to the two retro Diels–Alder fragments.

Additional evidence for [4 + 2⁺] cycloaddition comes from considering data on reactions of reagent ions other than simple alkyl-substituted acylium ions. These include some which are discussed in more detail in the sections which follow. One such case is provided by the α,β-unsaturated acylium ions (**13–16**) which fragment readily by loss of CO, a process which is confirmed by MS³ experiments. Similarly, CID fragmentation of the adduct of **17** yields PhC≡O⁺ and also eliminates HNCO, processes which we interpret as evidence for cycloaddition at the C=N bond, as discussed below. These results rule out the open-chain carbocation structures for which such fragmentations are unlikely. Additional evidence for the proposed Diels–Alder cycloaddition process comes from the behavior of the thioacetyl cation. In comparison with the acetyl ion, the sulfur analog is expected to have weaker bonds, and while reversion to the starting material is still the major product, the spectrum contained many other abundant products, which can be interpreted[5b] in terms of [4 + 2⁺] cycloaddition.

Finally, high-level *ab initio* molecular orbital calculations provide support for the proposed reaction by showing that the Diels–Alder cycloaddition process is the favored reaction between the acetyl cation and butadiene. These calculations were done at the MP2/6-31G** level, and they show the cyclic Diels–Alder product to be 114 kJ mol⁻¹ more stable than the C1-acetylation product. The C2-acetylation product is unstable relative to starting materials.

Alkyl-Substituted Acylium Ions. The formyl cation (**1**) does not display adduct formation in its ion/molecule product spectrum with isoprene because competitive proton transfer is greatly facilitated by the acidity of the hydrogen.[25] Proton transfer to isoprene by **1**, eq 1, is estimated[26] to be thermodynamically 259 kJ/mol more favorable than the corresponding process for the acetyl cation (**2**), eq 2. The formyl cation therefore undergoes proton-transfer reactions with a large variety of neutral compounds in the gase phase.[27]

$$HC{\equiv}O^+ + C_5H_8 \rightarrow CO + C_5H_9^+ \qquad (1)$$

$$H_3CC{\equiv}O^+ + C_5H_8 \rightarrow H_2C{=}C{=}O + C_5H_9^+ \qquad (2)$$

(23) The dimethylfulvene adduct displays in its MS³ spectrum (Table II) a much more abundant ion due to the protonated fulvene than that for the cycloreversion product. This suggests that this ion may not comprise the cycloaddition product exclusively.

(24) Paradisi, C.; Kenttämaa, H.; Le, Q. T.; Caserio, M. C. *Org. Mass Spectrom.* **1988**, *23*, 521.

(25) The proton affinities of some neutrals mentioned in the text are (in kJ/mol) CO (593), H_2CCO (828), H_3CNCS (819), HNCO (724), CO_2 (547): Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695.

(26) Value calculated using the following ΔH_f values (kJ/mol). 1 (825.6): Traeger, J. C. *Int. J. Mass Spectrom. Ion Processes* **1985**, *66*, 271. 2 (630): see ref 25. CO (–111): see ref 12. Ketene (–47.7): see ref 11a.

(27) (a) Gardner, M. P.; Vinckier, C. *Int. J. Mass Spectrom. Ion Processes* **1985**, *63*, 187. (b) Raksit, A. B.; Bohme, D. H. *Can. J. Chem.* **1985**, *63*, 854. (c) Clary, D. C.; Smith, D.; Adams, N. G. *Chem. Phys. Lett.* **1985**, *119*, 320.

Table III. Ion/Molecule Product Spectral Data for Reaction between the Acetyl Cation (2) and Some Neutral Reagents

		products m/z (relative abundance)[a]	
neutral reagent	adduct	charge exchange and/or proton transfer	other products[b]
styrene	147 (3)	104 (16), 105 (100)	91 (1), 94 (1), 117 (2)
benzene		78 (77), 79 (100)	75 (6), 91 (6), 93 (2),[c] 104 (9),[d] 105 (5)[d]
benzonitrile		104 (100)	87 (2), 118 (2), 207 (14)[e]
ethyl vinyl ether	115 (2)	72 (2), 73 (30)	87 (4),[f] 101 (100)[g]
1,3-butadiene	97 (100)	55 (1)	67 (8), 75 (2), 81 (4), 87 (2), 93 (11), 105 (2), 107 (4), 109 (5), 121 (2)[h]
cyclopentadiene	109 (100)	67 (5)	91 (2), 93 (3), 94 (4), 105 (4), 117 (5), 131 (10),[i] 133 (4),[i] 157 (7), 175 (4)
limonene	179 (0.5)	121 (100),[j] 135 (11), 137 (12)	81 (31), 93 (21), 95 (12), 101 (1), 107 (15), 109 (9), 161 (3)[k]
6,6-dimethylfulvene	149 (9)	107 (100)[l]	91 (1), 121 (1)
3-methylene-cyclohexene	137 (0.3)	95 (100), 189 (2)[m]	

[a] Relative to the major peak, excluding the reagent ion. [b] Some of these products are assigned as indicated. [c] The methylation product (see ref 13d) and its loss of H_2 fragment m/z 91. [d] Fragments of an unstable adduct, corresponding to loss of CH_4 (m/z 105) and CH_4 and H (m/z 104). [e] Proton-bound benzonitrile dimer. [f] Fragment of the adduct corresponding to loss of C_2H_4. [g] Ion m/z 101 arises from reaction of the protonated ethyl vinyl ether (m/z 73) with the neutral molecule; see: Kenttamaa, H.; Cooks, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 4122. [h] All products except the cycloadduct, m/z 97, are due to reaction between the proton transfer product, protonated 1,3-butadiene m/z 55, and neutral 1,3-butadiene. [i] The protonated cyclopentadiene dimer (m/z 133) and its H_2 loss fragment (m/z 131). [j] Fragment due to CH_4 loss from protonated limonene. [k] Fragment due to CH_4 loss from the intact adduct. [l] Protonated dimethylfulvene. [m] The protonated diene and its dimer.

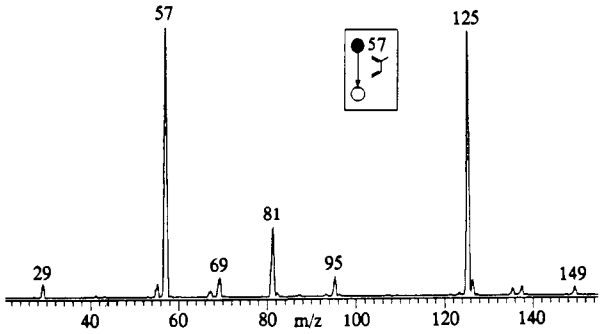


Figure 1. Ion/molecule product spectrum for reaction between the alkyl-substituted acylium ion 3 (m/z 57) and isoprene, showing the [4 + 2⁺] Diels–Alder cycloadduct (m/z 125), a fragmentation product (m/z 29), and the proton-transfer products (m/z 55, 69, 81, 95, 135, 137, and 149). The notation ● → ○ indicates that an analyzer passes a mass-selected ion (●) or scans over a range of masses (○); see ref 31.

The acylium ions **2–4** react readily with isoprene to form intact adducts ascribed to cycloaddition (Scheme I). This is exemplified in Figure 1 for ion **3**. In addition, proton transfer occurs and yields m/z 69, which, as noted above,[20] reacts with neutral isoprene to give a series of products including m/z 81, 95, 137, and 149.[5b] Fragmentation of the reactant acylium ions by CO loss occurs for ions **3** and **4**. Proton transfer is favored by the increase in the acidity of alkyl groups, while fragmentation is facilitated by the increase in stability of the carbenium ions which are generated upon loss of CO.[28]

The collision energy plays an important role in controlling the relative extent of occurrence of all three competitive processes. Even a slight increase in the collision energy from nominal 0 eV to approximately 1 eV[29] increases the extent of fragmentation and decreases the formation of the ion/molecule products; fragmentation becomes the predominant spectral feature at collision energies of 2 eV and higher. These are the expected results given that adduct formation occurs by an orbiting collision complex, the likelihood of which decreases sharply as the collision energy is increased, while the endothermic process of fragmentation is favored by increased collision energy.[30]

The MS^3 sequential product spectra[31] (Table II) of the cycloadducts were acquired by performing collision-induced dissociation (CID) with argon in the second collision quadrupole. These spectra, which display the products of dissociation of the cycloadducts of ions **2–4**, are remarkably simple. They show that these cycloaddition products fragment predominantly to the original acylium ions (Scheme I) by the retro Diels–Alder process.

Aryl-Substituted Acylium Ions. The acylium ion **5** bears a phenyl group and is therefore expected to display greater cycloaddition reactivity in both the normal and inverse electron demand Diels–Alder reactions due to the conjugation provided by the aromatic ring.[15] The phenyl group may also facilitate the reaction by stabilizing the ionic cycloadduct by charge delocalization. The results for ion **5** show that cycloaddition, which yields m/z 173, indeed occurs to a large extent (relative to proton transfer) and that the reaction is favored even when compared to that observed for the alkyl-substituted acylium ions. This can be seen by comparing the cycloadduct vs m/z 81 ratios displayed in Table I (17:1 for ion **5** and 10:1 for ion **2**). Ions **6** and **7**, which contain electron-donating (methoxy) and electron-withdrawing (nitro) substituents in the para position of the phenyl ring, also undergo cycloaddition (Table I). The MS^3 spectra of the cycloadducts formed from the aryl-substituted acetyl ions show the retro Diels–Alder process to be the major fragmentation pathway (Table II), accompanied in the case of **5** by the loss of propene.

Regioselectivity of the Cycloaddition Reaction. The acylium ions **8–12** contain π-electron-donating groups, Y, directly attached to the C≡O⁺ group. They represent an interesting case in terms of both reactivity and regioselectivity. These ions can be represented by two resonance structures ($YC{\equiv}O^+ \leftrightarrow {}^+Y{=}C{=}O$), and this emphasizes the fact that [4 + 2⁺] cycloaddition may occur at either the C≡O⁺ or ⁺Y=C bonds, leading to formation of either of the cycloadducts shown in Scheme III. However, charge delocalization can be expected in this case to stabilize the C≡O⁺ cycloadducts and to facilitate cycloaddition in this way.

This group of ions displays a range of reactivities with isoprene (Table I). Ions **8** and **10** react mainly by proton transfer, which is the favored reaction channel due to the relatively acidic hydrogen borne by these ions.[25] Among the other reactant ions, the $ClC{\equiv}O^+$ ion (**12**) does not show cycloadduct formation, its spectrum being dominated by ions due to charge exchange (formation of the radical cation of isoprene, m/z 68) and to products of subsequent reactions involving ionized and neutral isoprene.[32] The $H_3COC{\equiv}O^+$ ion (**11**) undergoes cycloaddition, and this reaction is predominant for the $(CH_3)_2NC{\equiv}O^+$ acylium ion (**9**). Therefore, the results show that cycloaddition is favored

(28) Rosenstock, H. M., Draxl, K.; Steiner, B. W.; Herron, J. T. *J. Phys. Chem. Ref. Data* **1977**, *6*, Suppl. 1.

(29) Reaction of the acetyl cation (2) with isoprene, performed in a Finnigan TSQ-700 triple-quadrupole mass spectrometer, showed results very similar to those obtained in the pentaquadrupole, except that the maximum yield of the ion/molecule products was obtained for collision energies ranging from nominal 1 to 2 eV. The adduct m/z 111, generated in the ion source by reaction of ion 2 with isoprene, displayed a 10-eV CID product spectrum very similar to the MS^3 spectra (Table II).

(30) Gioumousis, G.; Stevenson, D. P. *J. Chem. Phys.* **1958**, *29*, 294.

(31) Schwartz, J. C.; Wade, A. P.; Enke, C. G.; Cooks, R. G. *Anal. Chem.* **1990**, *62*, 1809.

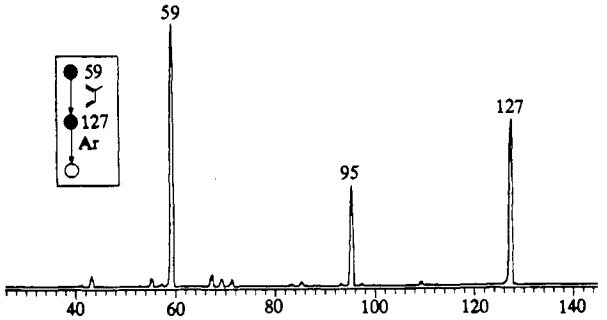
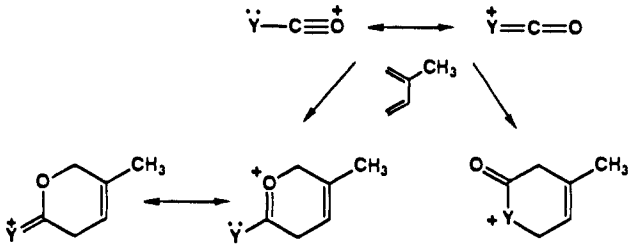


Figure 2. Sequential product MS^3 spectrum of the [4 + 2⁺] cycloadducts for the methoxy-substituted acylium ion **11**, showing CID fragmentation mainly by the retro Diels–Alder process (m/z 59) and by loss of methanol (m/z 95).

Scheme III



as the electron-donating ability of the substituents increases (Cl(none) ≪ OCH_3 < $N(CH_3)_2$), the same trend as is observed for inverse electron demand Diels–Alder reactions in solution.[15]

The MS^3 spectra for the cycloadducts m/z 140 (ion **9**) and m/z 127 (ion **11**) (Figure 2) display the retro Diels–Alder fragment as the major peak and show also other competitive fragmentation processes (Table II).

Another interesting case of reactivity and regioselectivity is presented by the α,β-unsaturated acylium ions **13–16**. In principle, these ions could react with isoprene by Diels–Alder cycloaddition at either the C=C and/or C≡O⁺ bonds. The conjugation provided by the C=C bond is expected to increase the cycloaddition reactivity at the C≡O⁺ bond, while the C=C bond is also expected to be strongly activated toward cycloaddition by the positively charged, electron-withdrawing C≡O⁺ group.

Ion **13** displays, in its ion/molecule product spectrum, both an intact adduct (m/z 123, low abundance) and a fragment ion at m/z 95 (Figure 3a) which corresponds to loss of a neutral fragment of mass 28 daltons from the adduct. The fact that this fragmentation pathway was not observed to any extent for the C≡O⁺ cycloadducts formed for the acylium ions discussed previously, even upon activation by 10-eV collisions with argon in the MS^3 experiments (Table II), and that it occurs to a very large extent here under the milder ion/molecule reaction conditions, indicates that the cycloaddition reaction takes place mainly at the C=C bond. The resulting cycloadduct m/z 123 has enough internal energy to fragment extensively by the facile process of CO loss to form the cyclic carbocation m/z 95 (Scheme IV). Note that extra stabilization of m/z 95 is possible by charge delocalization if hydrogen atom transfer occurs to generate the allylic cation as is expected.

Clear evidence for the hypothesis that cycloaddition occurs at the C=C bond of ion **13**, followed by loss of CO to form m/z 95, is provided by the MS^3 spectrum of m/z 55 (Figure 4a). This spectrum is virtually identical to the CID product spectrum of the m/z 95 ion formed by loss of a methyl radical from ionized 1,3-dimethylcyclohexene (Figure 4b). This latter ion is expected to be formed by allylic cleavage and hence to have the structure

(32) Reaction between ionized and neutral isoprene shows the same set of product ions observed in the reaction involving protonated isoprene; see footnote 20 and the following: Kascheres, C.; Cooks, R. G. *Anal. Chim. Acta* **1988**, *215*, 223.

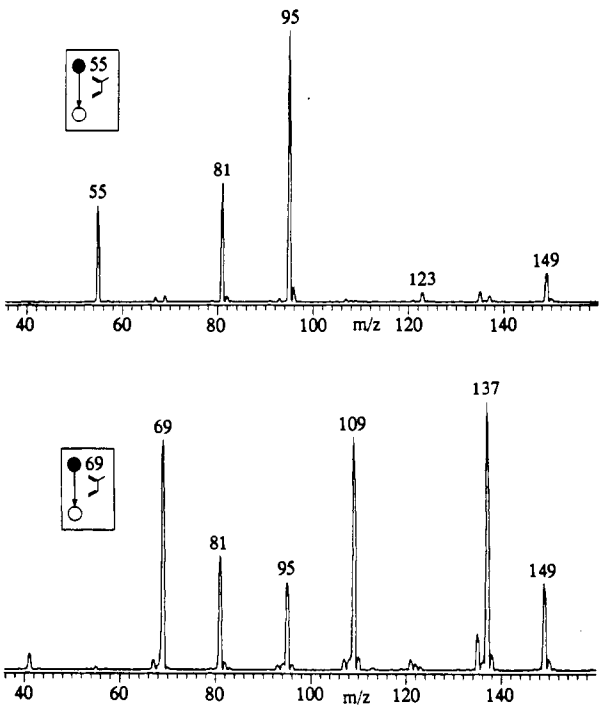
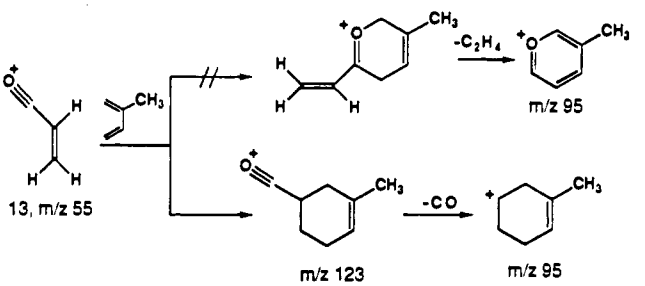


Figure 3. Ion/molecule product spectra for reaction between isoprene and (**a**) the α,β-unsaturated acylium ion **13**, displaying little of the intact adduct at m/z 123 and abundant decarbonylated cycloadduct at m/z 95, indicative of reaction at the C=C bond, and (**b**) the α-methyl-substituted α,β-unsaturated acylium ion **14**, showing abundant formation of both the intact and decarbonylated cycloadducts at m/z 137 and 109, respectively, indicative of reaction occurring at both the C≡O⁺ and C=C bonds.

Scheme IV



proposed for the m/z 95 ion/molecule product of C=C addition (Scheme IV). The fact that the two spectra displayed in Figure 4 are identical establishes the $C_7H_{11}^+$ composition of the ions undergoing fragmentation. This is also reflected in the series of neutral losses of molecular hydrogen (m/z 93), ethylene (m/z 67), ethylene and molecular hydrogen (m/z 65), and methylacetylene (m/z 55). The MS^3 data therefore confirm that the fragment at m/z 95 is the hydrocarbon, generated by loss of CO from the adduct; it does not allow the alternative interpretation, that m/z 95 retains the oxygen atom, which would be expected if cycloaddition had occurred at the C≡O⁺ group.

The large preference of the α,β-unsaturated acylium ion **13** to react at the C=C bond can be ascribed to activation of the double bond in the dienophile by the strong electron-withdrawing effect of the positively charged C≡O⁺ group.[15] An interesting parallel can be drawn to the solution-phase reactivity of ions H_2C=CHCH=O⁺R, which react readily at the C=C bond due to the activating effect of the positively-charged substituent.[3]

Substitution at the double bond of α,β-unsaturated acylium ions **14–16** causes remarkable changes in the regioselectivity of the cycloaddition reaction which, nevertheless, still occurs with facility (Table I). While ion **13** reacts almost exclusively at the C=C bond, forming the decarbonylated cycloadduct at m/z 95 (Figure 3a), as just discussed, the α-methyl-substituted ion **14**

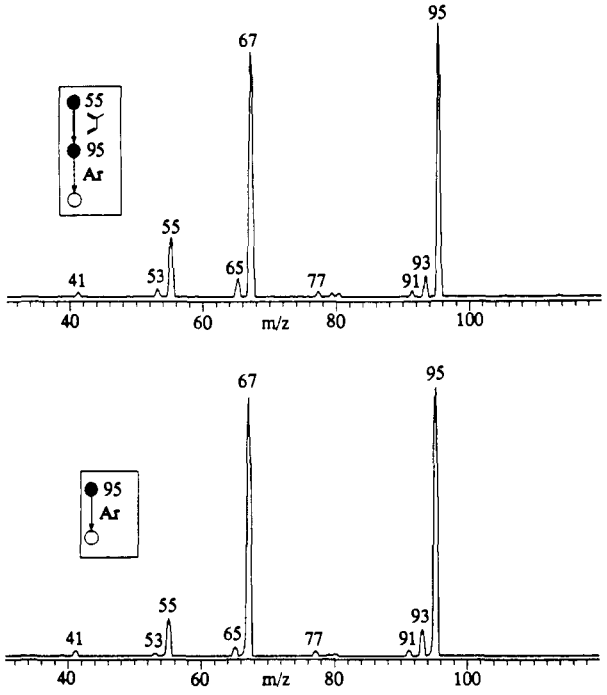


Figure 4. (a) Sequential product MS^3 spectrum of the decarbonylated $[4+2^+]$ cycloadduct m/z 95 for ion **13** and (b) MS^2 CID product spectrum of the fragment ion m/z 95 generated from ionized 1,3-dimethylcyclohexene.

reacts at both the C=C and C≡O$^+$ bonds to form the decarbonylated and intact cycloadducts at m/z 109 and 137, respectively, in approximately equal proportions (Figure 3b). α,β-Dimethyl (**15**) and α-isopropyl (**16**) substituents make the C=C bond much less reactive, and cycloaddition occurs predominantly at the C≡O$^+$ bond, yielding ions m/z 151 and 165, respectively (Table I). This trend can be understood as a result of deactivation of the C=C bond by the alkyl groups, although steric hindrance may also contribute. Evidence that ions m/z 137, 151, and 165 (generated from **14**, **15**, and **16**, respectively) consist predominantly of the C≡O$^+$ cycloadducts is obtained from their MS^3 spectra (Table II), which show the retro Diels–Alder fragment, and not the fragment due to loss of CO, as the major product.

The $C_8H_{13}^+$ and $C_9H_{15}^+$ compositions of the product ions m/z 109 (from **14**) and m/z 123 (from **15**), and hence their formation by loss of CO from the intact cycloadducts, are also clearly supported by the series of neutral loss fragments displayed in the MS^3 spectra (Table II). Even more direct support for the proposed site of reaction is the fact that the product spectrum for ion m/z 109 is *identical* to the CID product spectrum (not shown) of $C_8H_{13}^+$ (m/z 109) generated from 1,3-dimethylcyclohexene.

The C=N α,β-unsaturated acylium ion **17** reacts with isoprene to yield an abundant cycloadduct at m/z 200 (Table I). Loss of CO from the C=N cycloadduct would result in an unstable nitronium ion and therefore is not expected to occur (Scheme V). Both the C=N and C≡O$^+$ cycloadducts are candidates for the ion m/z 200, but the structure of the adduct is clearly elucidated by its rich MS^3 spectrum (Figure 5). This provides strong evidence for the formation of the C=N cycloadduct since the retro Diels–Alder fragmentation (m/z 132), which occurs as the main dissociation process for all the C≡O$^+$ cycloadducts so far encountered, is observed here only to a small extent. Loss of HNCO and fragmentation to yield PhC≡O$^+$ (m/z 105) are the main processes, both of which are reasonable only for the C=N cycloadduct, as discussed below. It is interesting to note that in the case of compound **17** both substituents, the phenyl group by conjugation and the C≡O$^+$ group as an electron-withdrawing substituent, are expected to activate the C=N double bond toward a normal Diels–Alder cycloaddition. This may in part explain

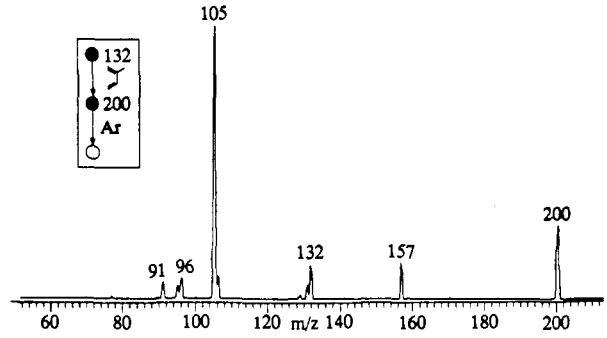


Figure 5. Sequential product MS^3 spectrum of the intact $[4+2^+]$ cycloadduct m/z 200 for the C=N α,β-unsaturated acylium ion **17** showing fragmentation to give PhC≡O$^+$ (m/z 105) and by loss of HNCO (m/z 157), both of which are indicative of cycloaddition at the C=N bond.

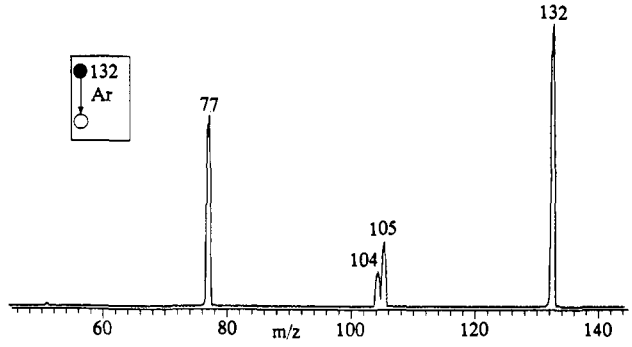
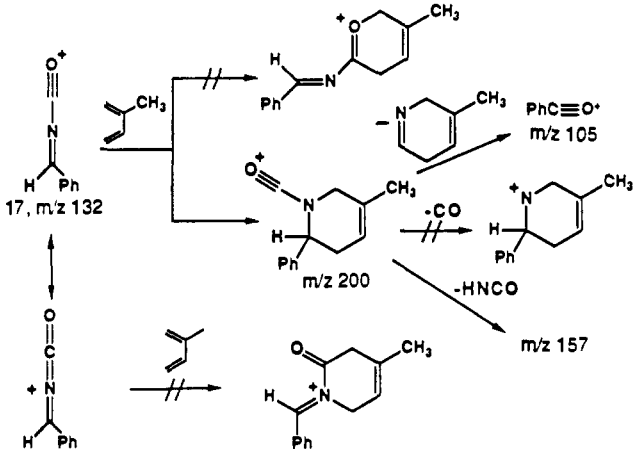


Figure 6. CID product spectrum of the C=N α,β-unsaturated acylium ion **17**, showing its fragmentation to PhC≡O$^+$ (m/z 105), PhHN$^+$=CH (m/z 104), and Ph$^+$ (m/z 77).

Scheme V

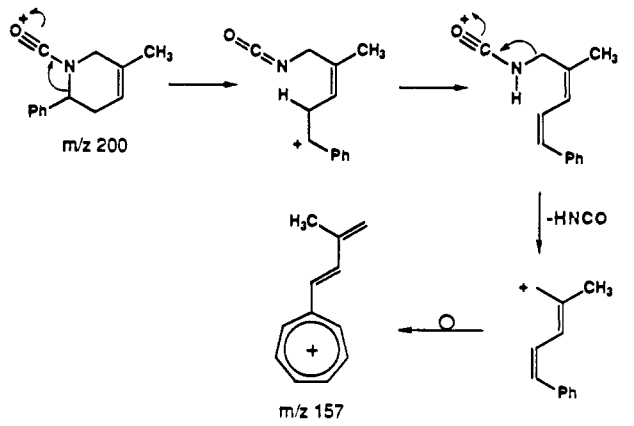


the very high cycloaddition reactivity displayed by this ion, the highest among all the ions investigated (Table I).

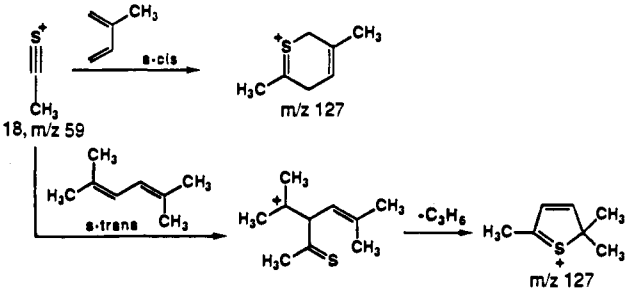
The PhC≡O$^+$ elimination from the C≡O$^+$ cycloadduct may occur with the participation of a four-membered cyclic intermediate, which may be compared to intermediates proposed when phenyl groups provide anchimeric assistance.[33] A similar dissociation process, yielding PhC≡O$^+$ (m/z 105), is also observed in the MS/MS CID product spectrum of ion **17** (Figure 6). The fact that the PhC≡O$^+$ cation (m/z 105), seen in the MS^3 sequential product spectrum of m/z 200 (Figure 5), is formed directly from m/z 200 and *not* by subsequent fragmentation of the retro Diels–Alder fragment, m/z 132, is evident from the CID product spectrum of m/z 132 (Figure 6), which shows m/z 77, and not m/z 105, as the major fragment ion and which shows

(33) March, J. *Advanced Organic Chemistry*; Wiley: New York, 1985.

Scheme VI



Scheme VII



also substantial formation of m/z 104, which is not observed in Figure 5. As a further test of this point, the collision gas pressure was varied in the MS^3 scan,[34] and it did not change significantly the relative abundance of ions m/z 132 and 105. A change would be expected to occur if m/z 105 was generated by two consecutive fragmentation processes (m/z 200 → m/z 132 → m/z 105).

Additional evidence which firmly points to the occurrence of mainly C=N cycloaddition for ion **17** is obtained from the fact that m/z 200 fragments to m/z 157, which is observed both in the ion/molecule product spectrum (Table I) and in the MS^3 spectrum of m/z 200 (Figure 5). The ion m/z 157 can be rationalized as the product of loss of HNCO from m/z 200, a fragmentation process which is expected for the C=N cycloadduct, but not for the $C{\equiv}O^+$ cycloadduct, and which can lead to formation of the stable, fully delocalized cation m/z 157 proposed in Scheme VI. Note the benzylic ring cleavage which is proposed as the initiating step in HNCO elimination.

Thioacetyl Cation. The thioacetyl cation (**18**), the sulfur analog of the acetyl cation (**2**), reacts as does its oxygen analog ion, predominantly by [4 + 2⁺] cycloaddition (Scheme VII), forming an abundant adduct at m/z 127 (Table I). It is interesting to note that ion **18** was not observed to react by cycloaddition with another diene, 2,5-dimethyl-2,4-hexadiene.[35] The main reaction observed[35] in that case was proton transfer, while a secondary reaction leads to formation of an ionic product at m/z 127 which was proposed to have the thiophene structure shown in Scheme VII. The lack of observation of the cycloadduct in this case is very likely due to the known low reactivity of this particular diene toward [4 + 2⁺] cycloaddition due to steric hindrance between the 2- and 5-methyl groups, which makes it difficult for this diene to assume the s-cis conformation required for Diels-Alder reaction.[15b]

The cycloadduct, m/z 127 formed from isoprene and the thioacetyl cation (**18**), displays a rich MS^3 sequential product spectrum (Table II). The main fragmentation processes correspond to loss of C_2H_4 (m/z 95), H_2S (m/z 95), and H_2S and CH_4 (m/z 79) and also to the retro Diels–Alder reaction (m/z 59).

Conclusion

These results provide strong evidence that many acylium ions undergo a previously unknown polar [4 + 2⁺] Diels–Alder cycloaddition reaction in the gas phase. The ion/molecule reaction product spectra, in combination with the information provided by MS^3 experiments, show how the cycloaddition reactivity and regioselectivity of acylium ions is controlled by the nature of the substituents. Addition at the carbonyl group is characterized by ready cycloreversion. α,β-Unsaturated acylium ions are activated by the carbonyl group and undergo [4 + 2⁺] cycloaddition at the C=C double bond and/or, depending on the substituents present, at the carbonyl group. MS^3 spectra, especially by elucidating the degree of cycloreversion and CO loss, allow these cases to be distinguished. The C=N cycloadduct for ion **17** displays a characteristic CID fragmentation dominated by $PhCO^+$ formation, while loss of HNCO and the retro Diels–Alder process are also observed. The relative abundance of the cycloadducts depends not only on the cycloaddition reactivity of the ion but also on the extent of occurrence of two competitive processes, proton transfer and fragmentation.

The ability of acylium ions to act as dienophiles in Diels–Alder cycloaddition reactions can be compared to their neutral isoelectronic counterparts, the nitriles, which react in solution with dienes to initially form 3,6-dihydropyridines.[1a] Several other types of even-electron cations are known to react in solution by polar Diels–Alder cycloadditions.[1-3]

The [4 + 2⁺] cycloaddition reaction with isoprene is shown here to serve as a method to clearly identify in the gas phase many members of the acylium ion class. Since completion of this study, a related MS^3 study of the reactions of acylium ions with 1,3-dioxolane[36] has shown that oxirane addition occurs (with accompanying elimination of a molecule of aldehyde). This reaction serves as another convenient method of characterizing acylium ions, and its occurrence under conditions similar to those used in the present study shows that other covalent ionic products can be generated from acylium ions under these reaction conditions. Both these reactions can be visualized as providing an approach to intercept, for detailed study, this important class of reaction intermediates. Although solvent effects cannot be easily estimated, it is possible that analogous cycloaddition reactions occur in solution.

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(34) The collision gas pressure (argon) was varied in order to cause depletion of the ion beam in the range of approximately 10%–90%.

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