

Mono and double polar [4 + 2⁺] Diels–Alder cycloaddition of acylium ions with O-heterodienes

Eduardo C. Meurer and Marcos N. Eberlin*

State University of Campinas–UNICAMP, Institute of Chemistry, CP 6154, 13083-970 Campinas, SP, Brazil

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Gas-phase reactions of acylium ions with α,β -unsaturated carbonyl compounds were investigated using pentaquadrupole multiple-stage mass spectrometry. With acrolein and metacrolein, $\text{CH}_3-\text{C}^+=\text{O}$, $\text{CH}_2=\text{CH}-\text{C}^+=\text{O}$, $\text{C}_6\text{H}_5-\text{C}^+=\text{O}$, and $(\text{CH}_3)_2\text{N}-\text{C}^+=\text{O}$ react to variable extents by mono and double polar [4 + 2⁺] Diels–Alder cycloaddition. With ethyl vinyl ketone, $\text{CH}_3-\text{C}^+=\text{O}$ reacts exclusively by proton transfer and $\text{C}_6\text{H}_5-\text{C}^+=\text{O}$ forms only the mono cycloadduct whereas $\text{CH}_2=\text{CH}-\text{C}^+=\text{O}$ and $(\text{CH}_3)_2\text{N}-\text{C}^+=\text{O}$ reacts to great extents by mono and double cycloaddition. The positively charged acylium ions are activated O-heterodienophiles, and mono cycloaddition occurs readily across their $\text{C}^+=\text{O}$ bonds to form resonance-stabilized 1,3-dioxinylium ions which, upon collisional activation, dissociate predominantly by retro-addition. The mono cycloadducts are also dienophiles activated by resonance-stabilized and chemically inert 1,3-dioxonium ion groups, hence they undergo a second cycloaddition across their polarized $\text{C}=\text{C}$ ring double bonds. ¹⁸O labeling and characteristic dissociations displayed by the double cycloadducts indicate the site and regioselectivity of double cycloaddition, which are corroborated by Becke3LYP/6–311++G(d,p) calculations. Most double cycloadducts dissociate by the loss of a RCO_2COR^1 molecule and by a pathway that reforms the acylium ion directly. The double cycloadduct of the thioacylium ion $(\text{CH}_3)_2\text{N}-\text{C}^+=\text{S}$ with acrolein dissociates to $(\text{CH}_3)_2\text{N}-\text{C}^+=\text{O}$ in a sulfur-by-oxygen replacement process intermediated by the cyclic monoadduct. The double cycloaddition can be viewed as a charge-remote type of polar [4 + 2⁺] Diels–Alder cycloaddition reaction. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: acylium ions; α,β -unsaturated carbonyl compounds; O-heterodienes; ion–molecule reactions; pentaquadrupole tandem mass spectrometry; polar [4 + 2⁺] Diels–Alder cycloaddition reactions

INTRODUCTION

Acylium ions are common and important ionic species both in solution¹ and in the gas phase.² When isolated in the diluted gas-phase environment, acylium ions are often stable and long-lived; hence, as for stable acylium ion salts,³ gaseous acylium ions can be easily formed and isolated so as to investigate their intrinsic properties and chemical reactivity. Recent multiple-stage mass spectrometric studies have investigated systematically the intrinsic reactivity of acylium ions, and have demonstrated the synthetic and analytical applications of their gas-phase reactions.^{4–13} Gaseous acylium ions undergo ketalization with diols and analogues⁴ and transacetalization with five- and six-membered ring acetals and ketals.⁵ With seven-membered ring acetals and ketals, acylium ions promote ring contraction,⁶ and sequential cyclization of acylium ions with two nitrile molecules forms 1,3,5-oxadiazinium ions.⁷

With epoxides, O-acylation is followed by ring expansion which forms 1,3-dioxolanylium ions.⁸ Halogen-activated acylium ions $\text{X}-\text{CO}^+$ ($\text{F} \gg \text{Cl} > \text{Br}$) promote carbonylation of benzene^{9,10} and five-membered heterocyclics¹⁰ via selective functionalization of their relatively inert $\text{C}-\text{H}$ ring bonds. Gaseous acylium ions also react with neutral amino acids by N-terminal derivatization followed by dissociation that produces structurally diagnostic modified b1 ions.¹¹ With amines (M), the benzoyl cation PhCO^+ yields characteristic $[\text{M} + \text{PhCO}]^+$, $[\text{M} - \text{NH}_2]^+$ and $[\text{PhCONH}_3]^+$ product ions with distributions characteristic of the amine environment.¹² Acylium ions also react with isomeric α -, β - and γ -hydroxyketones via structurally diagnostic cyclization reactions.¹³

In solution, cycloadditions are reactions of overwhelming synthetic usefulness, and have been the subject of many theoretical and mechanistic studies.¹⁴ Although cycloadditions occur efficiently for many uncharged or dipolar reactants, positively and negatively charged dienes and dienophiles are also employed as activated reactants in reactions known as polar cycloadditions.¹⁵ In the gas phase, polar cycloadditions have also been observed, and their mechanisms studied.^{16,17} Whether the gas-phase reactions occur in a concerted or stepwise fashion is difficult to

*Correspondence to: M. N. Eberlin, State University of Campinas–UNICAMP, Institute of Chemistry, CP 6154, 13083-970 Campinas, SP, Brazil. E-mail: eberlin@iqm.unicamp.br
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determine and hence this issue has been a subject of debate,¹⁸ but the usefulness of gas-phase cycloadditions for structural elucidation of ions and neutrals, for the gas-phase synthesis of cyclic ions, for class-selective ion-molecule reactions,¹⁹ and of gas-phase studies to access the intrinsic cycloaddition reactivity of ions with neutrals is unquestionable.

In the gas phase, acylium ions (R—C⁺=O) were found to act as strongly electron-deficient activated *O*-heterodienophiles, and to form 2,5-dihydropyrylium ions via unprecedented polar [4 + 2⁺] Diels–Alder cycloadditions with conjugated dienes.²⁰ Recently, additional evidence for the formation of cycloadducts has been collected as the presence of the 1-acetoxy group in the diene was found to favor cyclization with acylium ions followed by fast aromatization via the loss of a neutral acetic acid molecule to form aromatic pyrylium ions.²¹ Analogous polar [4 + 2⁺] Diels–Alder cycloadditions were also found to occur for gaseous nitrilium and immonium ions,²² as well as for protonated and methylated carbonyl compounds.²³

Via cycloaddition reactions, heterodienes have been employed efficiently for the solution synthesis of a variety of heterocyclic compounds.¹⁴ This paper reports on the gas-phase reactions of mass-selected acylium ions (*O*-heterodienophiles) with *O*-heterodienes, that is, α,β -unsaturated carbonyl compounds. Mono cycloaddition and also an unprecedented *double* polar [4 + 2⁺] Diels–Alder cycloaddition was observed. Mono cycloaddition occurs across the acylium ion C⁺=O bond to form resonance stabilized 1,3-dioxinylium ions. Double cycloaddition is site- and regioselective, and occurs across the C=C double bond of the mono cycloadduct in an interesting charge-remote²⁴ type of polar cycloaddition.

EXPERIMENTAL

Double-(MS²) and triple-stage (MS³) mass spectrometric experiments, performed with an Extrel (Pittsburgh, PA, USA) pentaquadrupole (Q₁Q₂Q₃Q₄Q₅) mass spectrometer,²⁵ were used to form the gaseous acylium ions, to react them with the carbonyl compounds and to characterize the product ions structurally. Appropriate precursors¹³ were used to form the reactant ions by 70 eV electron ionization: **1** and **3** (from methyl phenyl ketone), **2** (from ethyl vinyl ketone), **4** (from tetramethylurea) and **5** (from tetramethylthiourea).

The reactions were performed by MS² experiments where in which the acylium ion of interest was mass-selected by

Q1 for further reactions in q2 with the neutral carbonyl compound. Ion translational energies were set to near 1 eV as calibrated by the *m/z* 39 : 41 ratio in neutral ethylene/ionized ethylene reactions.²⁶ To record the product ion mass spectra, Q5 was scanned while operating Q3 in the broadband r.f.-only mode. Multiple collision conditions that caused typical beam attenuations of 50–70% were used in q2 so as to increase reaction yields and promote collisional quenching of both the reactant and product ions.²⁷

For the MS³ experiments,²⁸ a product ion formed in q2 was mass-selected by Q3 and further dissociated in q4 by 15 eV collision-induced dissociation (CID) with argon, while scanning Q5 to acquire the spectra. The 15 eV collision energy was taken as the voltage difference between the ion source and the collision quadrupoles. The indicated pressures in each differentially pumped region were typically 2 × 10⁻⁶ (ion-source), 8 × 10⁻⁶ (q2) and 8 × 10⁻⁵ (q4) torr (1 torr = 133.3 Pa).

Optimized geometries and energies of idealized conformations were obtained by theoretical calculations with no symmetry constraints using Becke3LYP²⁹ DFT/HF hybrid functionals and 6–311++G(d,p) basis sets as implemented in Gaussian 98.³⁰

RESULTS AND DISCUSSION

MS²

Four acylium ions (Ac⁺, R—C⁺=O), namely the acetyl cation **1** (R = CH₃), the acrylyl cation **2** (R = CH₂=CH), the benzoyl cation **3** (R = Ph) and the dimethyl carbamyl cation **4** (R = N(CH₃)₂), and three common *O*-heterodienes (M, R¹COC(R²)=CH₂), namely acrolein (R¹, R² = H), metacrolein (R¹ = H, R² = CH₃) and ethyl vinyl ketone (R¹ = C₂H₅, R² = H), were selected. Table 1 gives the corresponding product ion mass spectra and Fig. 1 shows, as an example, that for reactions of **4** with metacrolein.

Under the multiple collision conditions used, three major reactions were generally observed: mono polar [4 + 2⁺] Diels–Alder cycloaddition (MAc⁺) followed by a second cycloaddition (M₂Ac⁺), and proton transfer that forms MH⁺ and subsequently M₂H⁺. As evidenced by the characteristic dissociation behavior of the adducts and by ¹⁸O labeling, and as predicted by DFT calculations (see below), mono cycloaddition occurs as expected²⁰ across the acylium ion C⁺=O bond to form resonance stabilized 1,3-dioxinylium ions whereas double cycloaddition is site selective and occurs across the C=C double bond of the mono cycloadduct with

Table 1. Major product ions (*m/z* with relative abundances (%) in parentheses) for reactions of mass-selected acylium ions (Ac⁺) **1–4** with α,β -unsaturated carbonyl compounds (M)

Reactant ion	Acrolein			Metacrolein			Ethyl vinyl ketone		
	MAc ⁺	M ₂ Ac ⁺	MH ⁺ , M ₂ H ⁺	MAc ⁺	M ₂ Ac ⁺	MH ⁺ , M ₂ H ⁺	MAc ⁺	M ₂ Ac ⁺	MH ⁺ , M ₂ H ⁺
1	99 (4)	155 (15)	57 (3), 113 (100)	113 (14)	183 (6)	71 (36), 141 (100)	none	none	85 (75), 169 (100)
2	111 (14)	167 (26)	57 (1), 113 (100)	125 (20)	195 (100) ^a	141 (65)	139 (100)	223 (9)	85 (1), 169 (36)
3	161 (5)	217 (36)	57 (3), 113 (100)	175 (1)	245 (100)	141 (51)	189 (100)	none	85 (2), 169 (80)
4	128 (100)	184 (20)	113 (1)	142 (100)	212 (20)	141 (25)	156 (100)	240 (20)	169 (9)

^a In reactions of **2** with metacrolein, neutral loss (100 u) from M₂Ac⁺ of *m/z* 195 occurs extensively to form a product ion of *m/z* 95.

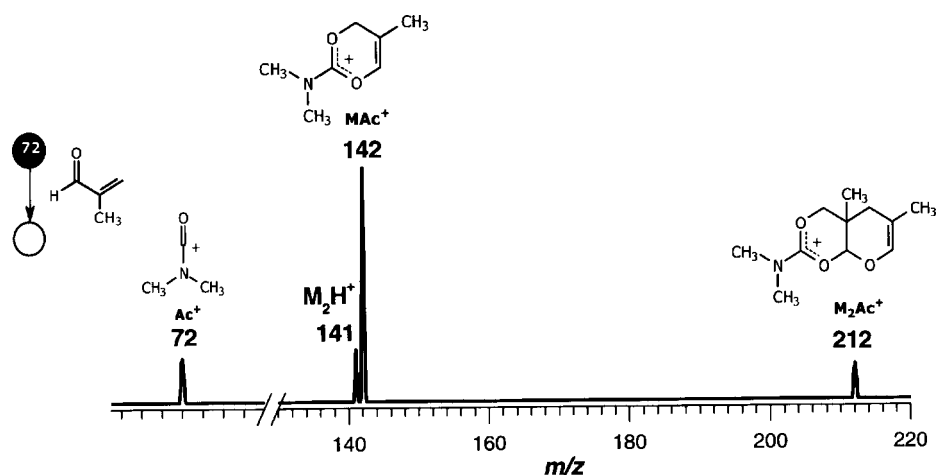
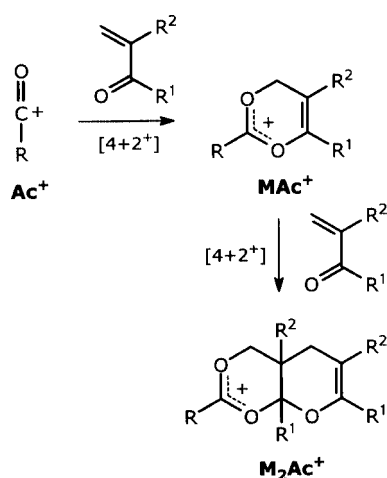


Figure 1. Double-stage (MS^2) product ion mass spectrum for reactions of the acylium ion **4** with metacrolein.



Scheme 1

the regiochemistry shown in Scheme 1. Because the charge site in the mono cycloadduct is considerably stabilized by resonance, the second cycloaddition is directed to the C=C double bond, which is activated by the electron-withdrawing positively charged substituent. The reaction can be considered, therefore, as a charge-remote²⁴ type of polar cycloaddition.

As exemplified for **4** of m/z 72 in Fig. 1, mono cycloaddition with metacrolein forms readily MAC^+ of m/z 142, which reacts further with a second metacrolein molecule by double cycloaddition to form M_2Ac^+ of m/z 212. The major proton transfer product is M_2H^+ of m/z 141. Because of the multiple collisions that the ions undergo inside the quadrupole reaction chamber, proton transfer that yields the protonated *O*-heterodiene (MH^+) may occur either from the reactant ion (Ac^+) or its product ions, or from both. MH^+ eventually reacts further with *M* to form the proton-bonded dimer M_2H^+ .

With acrolein and metacrolein, the four acylium ions tested react to variable extents by both mono and double cycloaddition (Table 1). For the proclivity to form cycloadducts, as compared with that to form the proton transfer products, **1** is the least reactive, **2** and **3** show medium reactivity and **4** is the most reactive. With ethyl vinyl ketone, **1** reacts exclusively by proton transfer, **3** forms

only the mono cycloadduct and **2** and **4** react to great extents by mono and double cycloaddition.

MS^3

The structures of the putative mono and double cycloadducts were investigated by collecting their triple-stage sequential product ion mass spectra. As often observed for the cycloadducts of acylium ions with dienes,²⁰ the mono cycloadducts dissociate exclusively by retro-addition to reform the acylium ion. Dissociation of the double cycloadducts of **2** (Fig. 2(c)) and **4** with ethyl vinyl ketone also occurs exclusively by retro-addition which reforms the mono cycloadduct and then the acylium ion by sequential losses of two molecules of ethyl vinyl ketone.

Dissociation of the acrolein and metacrolein double cycloadducts is, however, richer and more structurally elucidative, as exemplified in Fig 2(a) and (b) for those of **2**. Dissociation occurs mainly by retro-addition that reforms **2** of m/z 55 and, except for **1** (Figs 2(a) and 4(b)), this dissociation is apparently direct, that is, it occurs with no or little intermediacy of the mono cycloadduct. Dissociation also occurs, however, by a unique pathway involving the loss of a neutral molecule of 100 u that forms the fragment ions of m/z 67 and 95, respectively. Such a dissociation (Scheme 2) is structurally elucidative since it can be reasonably rationalized only for the double polar $[4 + 2^+]$ cycloadduct formed when the second cycloaddition occurs across the ring C=C double bond (Scheme 1).

Direct dissociation of both m/z 167 and 195 ions to re-form the reactant ion of m/z 55 is also consistent with the proposed structure of the double cycloadducts (Scheme 1) because it indicates that the second cycloaddition occurs neither at the vinyl group nor at the carbonyl group, and hence that the reactant acylium ion can be easily reformed directly from the double cycloadduct with a dissociation behavior characteristic of cyclic 1,3-dioxonium ions (Scheme 3).^{4,5}

Similar dissociation behavior is also observed for the acrolein and metacrolein double cycloadducts of **1**, **3** and **4**, as exemplified in Fig. 3 for those with metacrolein. Direct dissociation reforms the corresponding reactant acylium ions whereas loss of the corresponding RCO_2COH

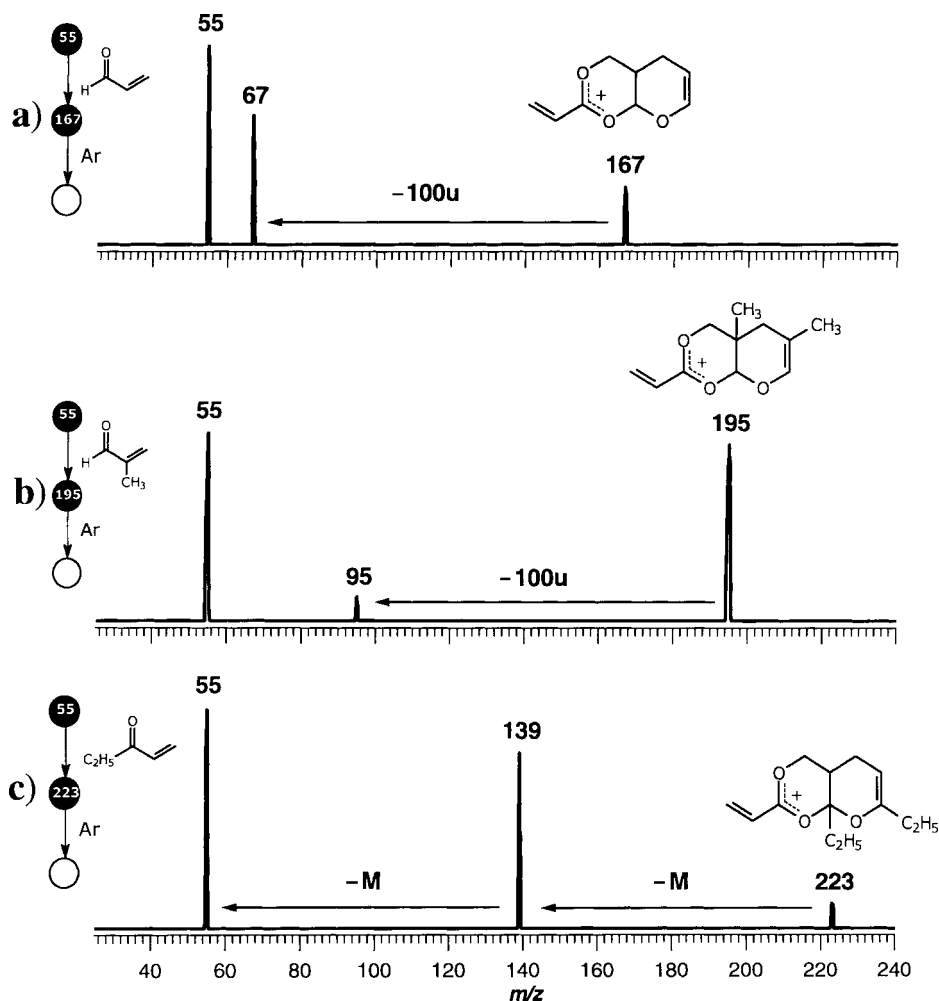
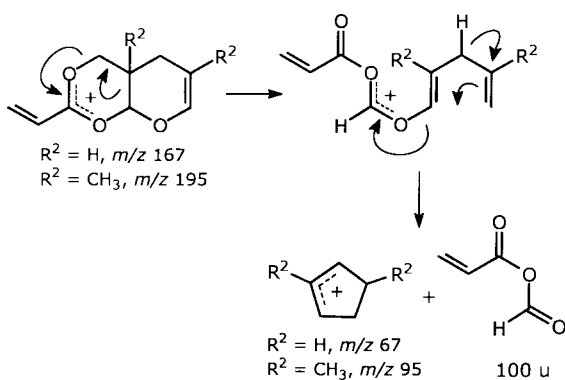
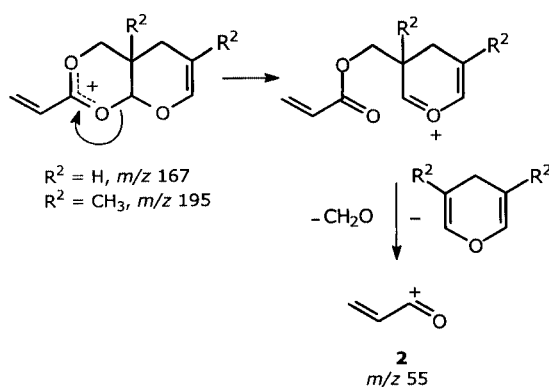


Figure 2. Triple-stage (MS^3) sequential CID product ion mass spectra of the double cycloadducts formed in reactions of the acylium ion **2** (m/z 55) with (a) acrolein, (b) metacrolein and (c) ethyl vinyl ketone.



Scheme 2

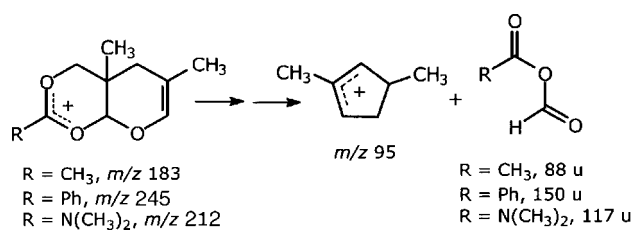


Scheme 3

neutral molecule yields the common fragment ion of m/z 95 (Scheme 4).

¹⁸O labeling

Evidence for the cyclic structure of the double adducts was also provided by ¹⁸O labeling. The labeled acetyl cation $CH_3-C^+=^{18}O$ of m/z 45 was formed by 70 eV EI of [¹⁸O] acetone,^{20a} reacted with acrolein and metacrolein, and the sequential product ion mass spectra of its mono and double cycloadducts were collected. As seen in Fig. 4



Scheme 4

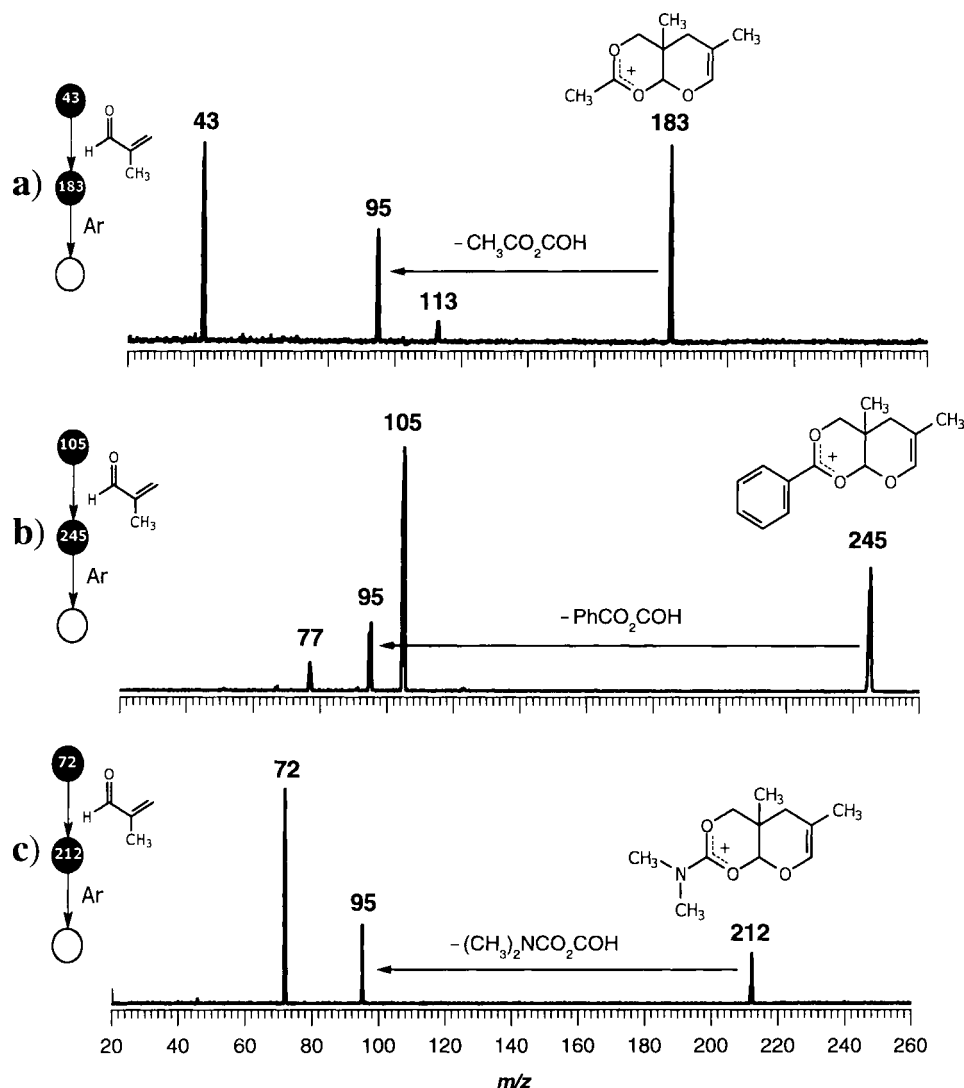
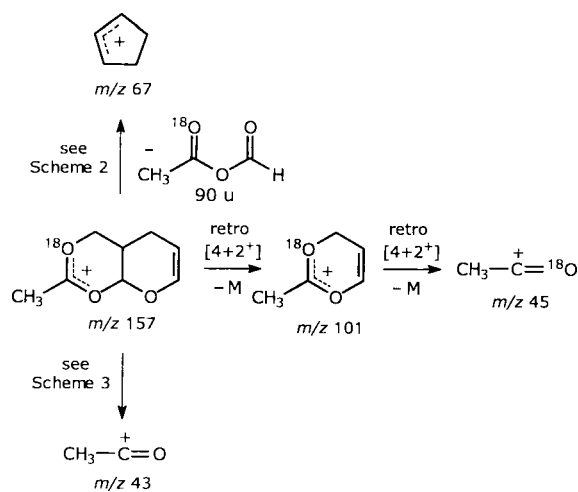


Figure 3. Triple-stage (MS^3) sequential product ion mass spectra of the double cycloadducts formed in reactions with metacrolein of the acylium ion (a) **1**, (b) **3**, and (c) **4**.

for those with acrolein, the mono cycloadduct dissociates exclusively to reform the labeled ion $CH_3-C^+=^{18}O$ of m/z 45 (Fig. 4(a)). This is the expected result of a normal retro-addition dissociation.²⁰ The double cycloadduct dissociates to m/z 101, 67, 45 and, most interestingly, m/z 43 (Fig. 4(b)). Dissociation to m/z 67 (Scheme 5) confirms the site- and regiochemistry-characteristic loss of RCO_2COH (Scheme 2). Retro-addition dissociation reforms the ^{18}O -mono cycloadduct of m/z 101, which then dissociates exclusively (see Fig. 4(a)) to $CH_3-C^+=^{18}O$ of m/z 45. The m/z 43 fragment is interesting since it corresponds to the unlabeled acetyl cation $CH_3-C^+=O$. Its formation (Scheme 5) can be easily rationalized only with the intermediacy of both the mono and double cycloadducts, whose formation promotes O-scrambling,²⁷ and direct dissociation of the double cycloadduct to re-form the unlabeled ion as generally depicted in Scheme 3.

Sulfur-by-oxygen replacement

Evidence for cyclic adducts was also obtained by reacting a thioacylium ion. Ion **5**, $(CH_3)_2N-C^+=S$, formed



Scheme 5

by 70 eV EI of tetramethylthiourea, was reacted with acrolein, and the mono (m/z 158, 100%), double (m/z 228, 18%) and, in this case, even the triple cycloadduct

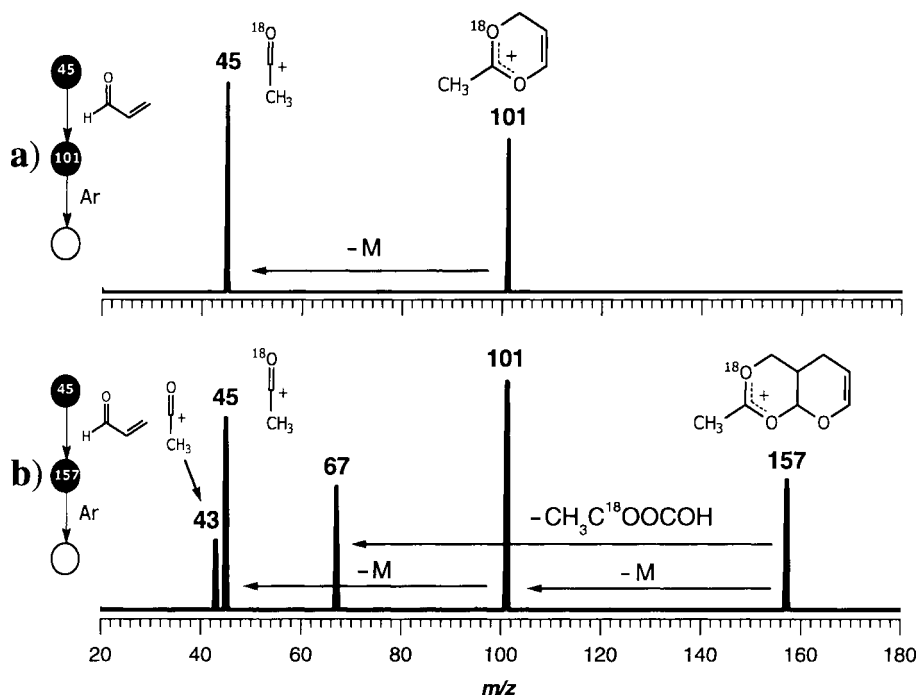
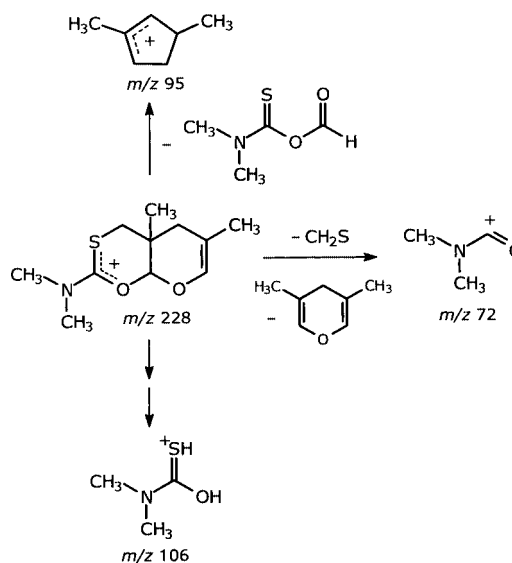


Figure 4. Triple-stage (MS^3) sequential CID product ion mass spectra of the (a) mono and (b) double cycloadducts formed in reactions of the labeled acylium ion **1** ($CH_3 - C^+ = {}^{18}O$) with acrolein.

(m/z 298, 33%) were formed readily (spectrum not shown). Figure 5 displays the triple-stage sequential product ion mass spectra of the double cycloadduct of m/z 228. Dissociation to m/z 95 occurs via the site- and regiochemistry-characteristic loss of $(CH_3)_2NCSOCOH$ of 133 u whereas the double cycloadduct also appears to dissociate to protonated dimethylthiocarbamic acid of m/z 106 (Scheme 6). The major and also the most structurally revealing fragment is that of m/z 72, which corresponds to **4**, the acylium ion analog of the reactant thioacylium ion **5**. Formation of m/z 72 can again be rationalized only with the intermediacy of both the mono and double cycloadducts, the formation of which allows for S-by-O replacement,³¹ and with the direct dissociation of the double cycloadduct to **4** (Scheme 6). The mono and triple cycloadducts of **5** with metacrolein also dissociate predominantly to **4**, which provides additional evidence for cyclic adducts.



Scheme 6

Theoretical calculations: reaction enthalpies

Figure 6 shows a potential energy surface diagram for a model reaction, that of **2** with two molecules of acrolein. Mono cycloaddition is found to be a favored, $-34.5 \text{ kcal mol}^{-1}$ exothermic reaction ($1 \text{ kcal} = 4.184 \text{ kJ}$). Double cycloaddition could then lead to a number of cycloadducts, and the four most likely alternatives (a–d) were considered. Cycloaddition across the C=C double bond (a) is predicted to be the most thermodynamically favorable, a reaction which is overall exothermic by as much as $-64.7 \text{ kcal mol}^{-1}$. Polar [4 + 2⁺] cycloaddition across the C=C bond of the 2-vinyl group (b) or at the C⁺=O ring bond (c) as well as polar [4⁺+2] cycloaddition across the C=C acrolein bond (d)

are not so favored, probably because the corresponding cycloadducts display a decreased degree of charge delocalization.

The mono cycloadducts bear highly stabilized 1,3-dioxonium ion groups, and such ions have been observed to be chemically inert species.^{5,27} However, the presence of the additional, non-conjugated ring C=C double bond activated by the strong electron-withdrawing, positively charged 1,3-dioxonium ion group confers on the mono cycloadducts a strong dienophile character. Their C=C ring bonds are also correctly polarized by inductive effects for double [4 + 2⁺] polar cycloaddition with O-heterodienes to occur with the observed regioselectivity (Scheme 1).

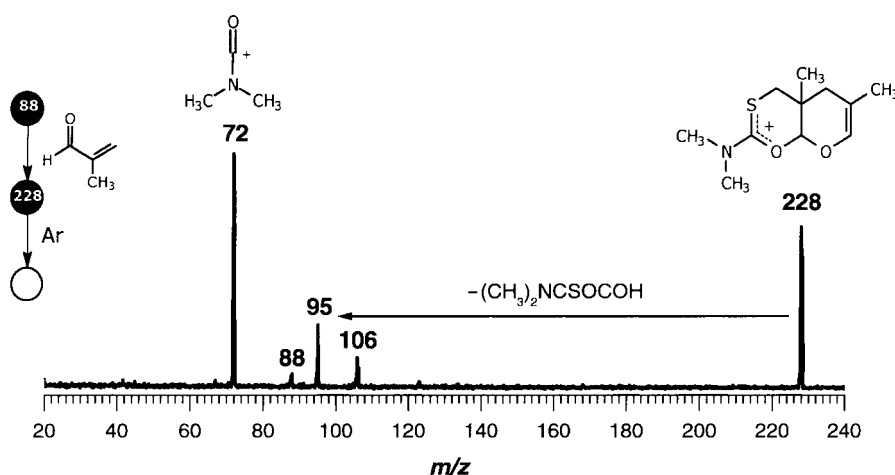


Figure 5. Triple-stage (MS^3) sequential CID product ion mass spectrum of the double cycloadduct formed in reactions of the thioacylium ion **5** (m/z 88) with metacrolein.

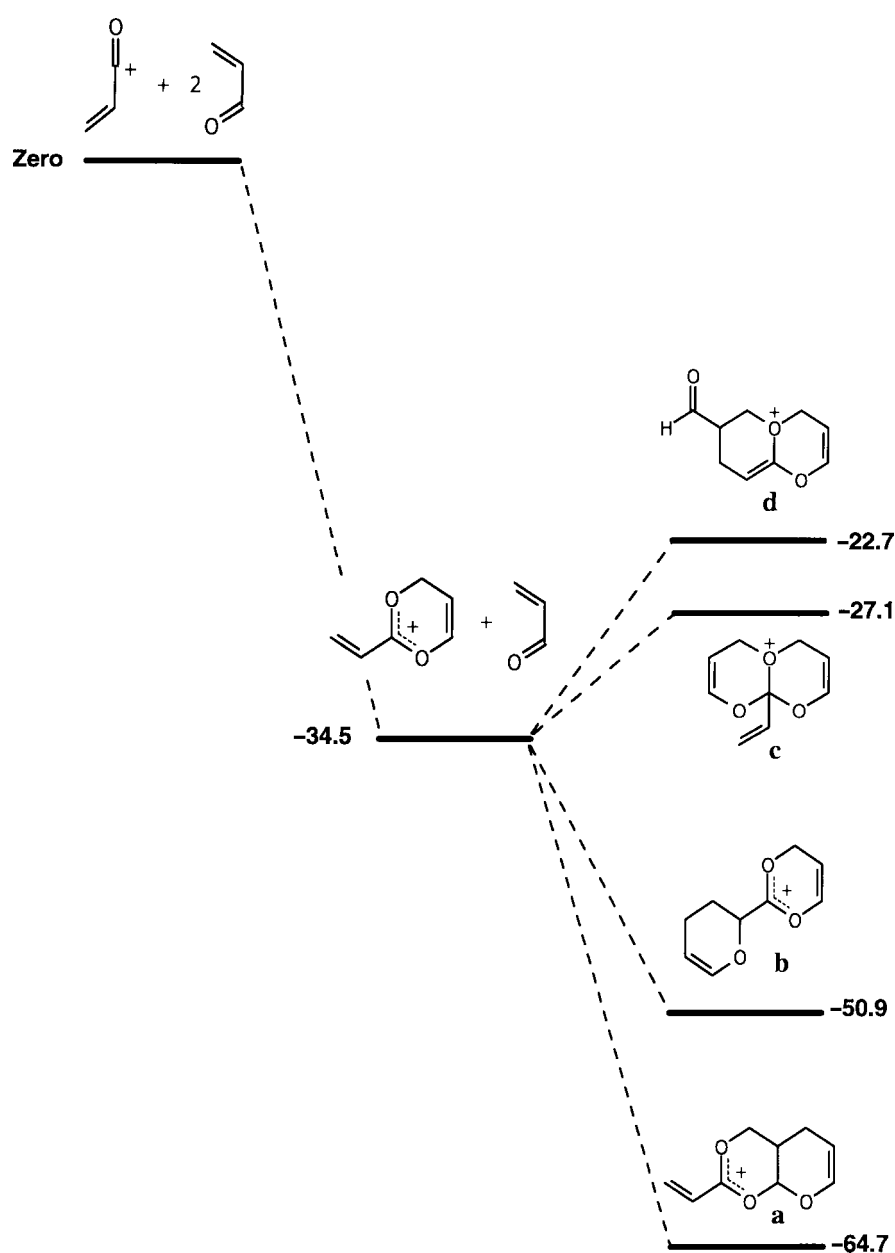


Figure 6. Becke3LYP/6-311++G(d,p) potential energy surface diagram for sequential cycloadditions of the acylium ion **2** with two molecules of acrolein. Reaction barriers were not estimated. The energies of the species are as follows: **2**, -191.06336; acrolein, -191.97079; mono cycloadduct, -575.05995; **a**, -575.10811; **b**, -575.08611; **c**, -575.04813; and **d**, -575.04114 hartree.

CONCLUSION

Gaseous acylium ions react to variable extents with α , β -unsaturated carbonyl compounds (O-heterodienes) by mono and double polar [4 + 2⁺] Diels–Alder cycloadditions. The positively charged acylium ions are activated O-heterodienophiles, and mono cycloaddition occurs readily across their C⁺=O bond to form resonance-stabilized 1,3-dioxynilium ions, which dissociate predominantly upon CID by retro-addition. The mono cycloadducts are also dienophiles activated by resonance-stabilized, chemically inert and positively charged 1,3-dioxonium ion groups, hence they undergo a second cycloaddition across their activated and polarized C=C ring double bonds. ¹⁸O labeling and the characteristic dissociations of the double cycloadducts reveal the site- and regioselectivity of the double cycloaddition, which is also corroborated by Becke3LYP/6–311++G(d,p) calculations.

Cations with charge-stabilized sites are known to undergo charge-remote fragmentations,²⁴ that is, fragmentations which are independent of, and occur at locations far from, the charge site. By analogy, therefore, the mono cycloadducts with charge-stabilized and chemically inert charge sites can also be viewed as undergoing a type of charge-remote reaction, more specifically, a charge-remote polar [4 + 2⁺] Diels–Alder cycloaddition.

Acknowledgements

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