

The atmospheric pressure Meerwein reaction

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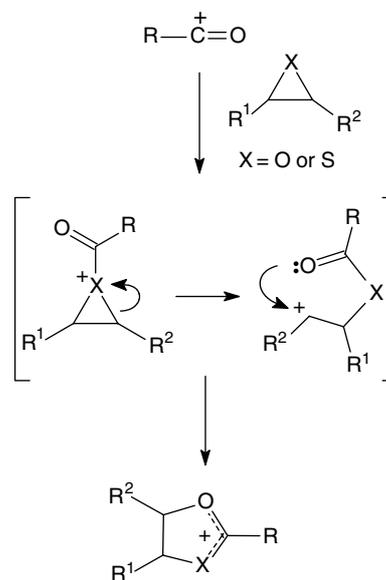
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We have already shown that the in-vacuum gas-phase Meerwein reaction of (thio)acylium ions is general in nature and useful for class-selective screening of cyclic (thio)epoxides. Herein we report that this gas-phase reaction can also be performed efficiently at atmospheric pressure under both electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) conditions. This alternative expands the range of molecules that can be reacted by gas-phase Meerwein reaction. Phenyl epoxide, thiirane, 3-methoxy-2,2-dimethyloxirane, propylene oxide, 2,2'-bioxirane, *trans*-1,3-diphenyl-2,3-epoxypropan-1-one, epichloridrine and propylene oxide are shown to react efficiently in both ESI and APCI conditions. Tetramethylurea (TMU) and (thio)TMU were both used as dopants, being co-injected with either toluene, acetonitrile or methanol solutions of the (thio)epoxides, with similar results. In both ESI and APCI, (thio)TMU is protonated preferentially, and these labile species dissociate promptly to yield $(\text{CH}_3)_2\text{N}-\text{C}^+=\text{O}$ and $(\text{CH}_3)_2\text{NCS}^+$, which are the least acidic and most reactive (thio)acylium ions so far tested in the gas-phase Meerwein reaction. Under the low-energy ESI conditions set to favor both the formation of the (thio)acylium ion and ion/molecule reactions, $(\text{CH}_3)_2\text{NCO}(\text{S})^+$ react competitively with (thio)TMU to form acylated (thio)TMU and with the (thio)epoxide to form the characteristic Meerwein products. Enhanced selectivity in structural characterization or for the screening of (thio)epoxides is achieved by performing on-line collision-induced dissociation of Meerwein products, particularly for the more structurally complex (thio)epoxides. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: class-selective ion/molecule reactions; gaseous acylium ions; (thio)epoxides; Meerwein reaction; ESI mass spectrometry

INTRODUCTION

(Thio)epoxides are very common reagents or key intermediates in a wide variety of synthetically important condensed-phase reactions.¹ In the gas phase, the Meerwein reaction with (thio)epoxides² (Scheme 1) is one of the most favored reactions of gaseous acylium ions.³ This class-selective reaction⁴ displays many features common to those of transacetalization reactions of (thio)acylium ions with (thio)acetals and analogs⁵ and is analogous to the condensed-phase reaction described in 1955 by Meerwein.⁶ It promotes expansion of the (thio)epoxide ring and is useful for both the characterization and selective screening of (thio)epoxides, including explosives and warfare agents.⁷ To perform such reactions in vacuum for mass-selected (thio)acylium ions, the neutral (thio)epoxides must be sufficiently volatile for its vapor to fill the collision cell region inside the mass spectrometer at the required concentration. Lack of proper volatility has therefore been a major limitation for the more general



Scheme 1

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applications of the gas-phase Meerwein reaction for heavier and less volatile (thio)epoxides.

In the gas phase, the intrinsic reactivity of gaseous (thio)acylium ions has been systematically investigated and

interesting synthetic and analytical applications of their reactions have been found. For instance, gaseous acylium ions react with dienes by polar $[4 + 2^+]$ cycloaddition,^{8–10} and undergo polar acetalization with diols and analogs^{11,12} and polar transacetalization with five- and six-membered cyclic acetals.^{13,14} Acylium ions also promote ring contraction of seven-membered acetals¹⁵ and undergo sequential cyclization with two nitrile molecules to yield 1,3,5-oxadiazinium ions.¹⁶ The gas-phase Meerwein reaction of (thio)acylium ions with (thio)epoxides yields cyclic 1,3-dioxolanylium ions.² Halogen acylium ions $X-CO^+$ ($F > Cl \gg Br$) promote carbonylation of benzene and of five-membered heterocyclics via selective functionalization of C–H aromatic bonds.^{17,18} Gaseous acylium ions also react with neutral peptides by *N*-terminal derivatization followed by dissociation, which produces structurally diagnostic, modified b_1 sequence ions.¹⁹ $PhCO^+$ also reacts with amines (M) yielding a characteristic set of $[M + PhCO]^+$, $[M + NH_2R]^+$ and $[PhCONH_3]^+$ product ions in proportions that are characteristic of the amine type.²⁰ With isomeric α -, β - and γ -hydroxyketones, acylium ions react via structurally diagnostic cyclization reactions,²¹ and with α -, β -unsaturated carbonyl compounds via single and double polar $[4 + 2^+]$ Diels–Alder cycloadditions.²²

Recently,²³ we began with polar transacetalizations to explore the interesting perspective of performing most, hopefully all, of these structurally diagnostic reactions⁴ of gaseous acylium ions under the atmospheric pressure conditions of both electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI). In this study we report that the gas-phase Meerwein reaction² also occurs efficiently under the atmospheric pressure conditions of both ESI and APCI.

EXPERIMENTAL

Gaseous $(CH_3)_2NCO^+$ and $(CH_3)_2NCS^+$ were chosen for this study as we have observed that these two (thio)acylium ions react most efficiently by the gas-phase reactions just described. They are also easily produced by the prompt dissociation of protonated (thio)tetramethylurea TMU molecules under both ESI and APCI conditions.²³

These (thio)acylium ions react quite efficiently with neutral (thio)epoxides in both ESI and APCI sources, and the products of the reactions were analyzed with either single (MS) or double-stage (MS^2) mass spectrometric experiments performed with a tandem QTOF (Manchester, UK) hybrid (quadrupole (Q), hexapole collision cell, time-of-flight (TOF)) mass spectrometer.²⁴ Solutions of (thio)epoxides (phenyl epoxide, propylene sulfide, 3-methoxy-2,2-dimethyloxirane, propylene oxide, 2,2'-bioxirane, *trans*-1,3-diphenyl-2,3-epoxypropan-1-one, epichloridrine and propylene oxide) were prepared in toluene or methanol and doped with (thio)TMU (1 mg of the acetal and 1 μ l of (thio)TMU dissolved in 1.5 ml of solvent). To form the (thio)acylium ions with the highest efficiency possible and to increase their residential time within the ion-source region so as to favor their low-energy reactions near atmospheric pressure collisions with the neutral acetal, cone and extractor voltages were set to 1 V and 40 V, respectively, whereas needle (ESI) voltages were both set at 4000 V.²³ For the MS^2 experiments, the product ion of interest was mass-selected by the first quadrupole mass filter and further subjected to 15 eV collision-induced dissociation (CID) with nitrogen in the hexapole collision cell, whereas the mass analysis was performed by the orthogonal-reflector TOF analyzer.

RESULTS AND DISCUSSION

Atmospheric pressure Meerwein reaction under ESI and APCI environments

Since protonated (TMU) dissociates promptly upon collisional activation, we use it as the dopant to form the desirable acylium ion $(CH_3)_2NCO^+$. This acylium ion is also of relatively low acidity,²⁵ hence the use of TMU as the dopant was also meant to minimize undesirable proton transfer reactions that would otherwise promote structurally unspecific protonation of the (thio)epoxide.

ESI-MS (as well as APCI-MS) of a methanolic solution of TMU (Fig. 1) yields both the protonated TMU of m/z 117 and the acylium ion $(CH_3)_2NCO^+$ of m/z 72. Note that similar spectra were acquired using toluene and acetonitrile solutions of TMU. $(CH_3)_2NCO^+$ is the most reactive acylium

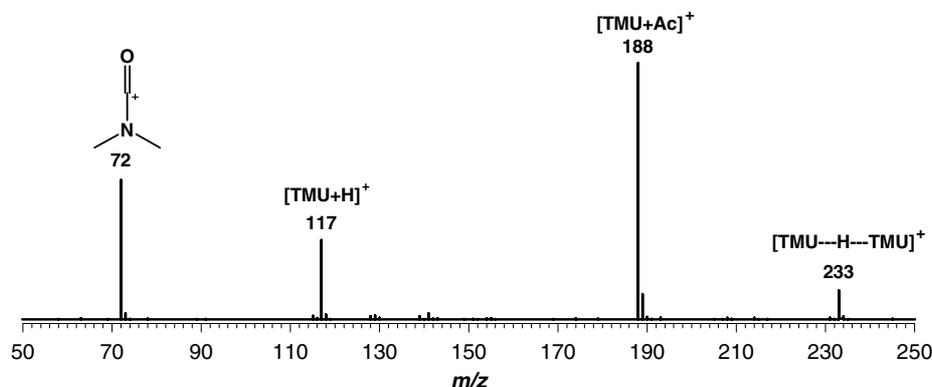


Figure 1. ESI-MS for a methanolic solution of TMU acquired using low-energy conditions that were optimized to favor both dissociation of protonated TMU of m/z 117 to the $(CH_3)_2NCO^+$ acylium ion (Ac^+) and atmospheric pressure ion/molecule reactions. The acylium ion of m/z 72 reacts with TMU to form acylated TMU of m/z 188. Protonated TMU also reacts with neutral TMU to form its proton-bound dimer of m/z 233. Similar spectra were obtained under APCI conditions and for solutions of TMU in toluene.

ion that we have so far tested in gas-phase reactions.²⁶ In the atmospheric pressure ESI environment and under the low ion-energy conditions used to maximize ion/molecule reactions, both the TMU-(CH₃)₂NCO⁺ adduct of *m/z* 188 and the TMU proton-bound dimer [TMU---H⁺---TMU] of *m/z* 233 are readily formed. An appropriate atmospheric pressure ESI environment for ion/molecule reactions, in which both prompt dissociation of [TMU + H]⁺ to (CH₃)₂NCO⁺ as well as efficient low-energy atmospheric pressure ion/molecule reactions occur, are thus established.

Using the ESI optimized conditions just described, we first performed reactions with the structurally simple, low mass, volatile epoxides **1** and **3** as well as the thio epoxide **2** (as proof of principle examples). Because the abundance of the Meerwein products relative to the ions arising from 'self-TMU' reactions (Fig. 1) depends on the relative concentrations of TMU and the (thio)epoxide, spectrum subtraction is desirable as it eliminates these common background product ions of variable abundances.

As the spectrum in Fig. 2 shows, both solutions of **1** or **2** doped with TMU yield ESI-MS in which essentially a single additional product ion is detected after TMU-background subtraction. The ions of *m/z* 192 and 146 are the expected Meerwein products, that is, the cyclic ionic acetals formed by expansion of the (thio)epoxide ring after O-acylation (Scheme 1).² Interestingly, neither proton transfer nor hydride abstraction products are formed. These structurally unspecific reactions are likely minimized as the result of quenching (collisional cooling) of both the reactant acylium ion and the Meerwein products under nearly atmospheric pressure conditions. For the in-vacuum reactions of gaseous acylium ions performed in quadrupole collision cells,²⁷ proton transfer and hydride abstraction often compete with Meerwein reactions.⁶

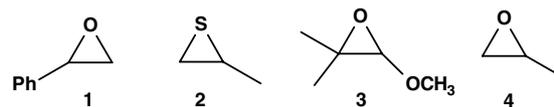


Figure 3 shows ESI-MS/MS for CID of the Meerwein products of **1**–**3**. When mass-selected and subjected to low-energy (10–20 eV) collisions with argon in the collision cell of the tandem QTOF mass spectrometer, these Meerwein products dissociate mainly to re-form the precursor acylium ion of *m/z* 72, as clearly seen for the ion of *m/z* 146 from **2** (Fig. 3(a)). Increased structural complexity with the presence of other functional groups or substituents (when placed at positions that favor specific bond cleavages) induces other competitive dissociations, as exemplified for the Meerwein product of *m/z* 174 from **3** (Fig. 3(b)). This ion dissociates competitively by *N,N*-dimethylcarbamic acid loss to form an abundant fragment ion of *m/z* 85. As expected, the Meerwein product of *m/z* 192 from **1** (Fig. 3(c)) dissociates predominantly to the precursor acylium ion of *m/z* 72, but it also forms a minor fragment ion of *m/z* 90 (protonated *N,N*-dimethylcarbamic acid). The same dissociation pattern has been observed for this ion when formed via polar transacetalization under both atmospheric pressure ESI²³ and in-vacuum conditions.²

The cyclic structures of the Meerwein products

The formation of cyclic products has been determined for the in-vacuum Meerwein reaction via CID and labeling experiments.² To test whether the same cyclic ionic acetals would be formed under atmospheric pressure ESI conditions, a solution of epoxide **4** doped with thio-TMU was electro-sprayed. As expected, an abundant Meerwein product of *m/z* 146 (Scheme 2) from reactions of (CH₃)₂NCS⁺ was formed

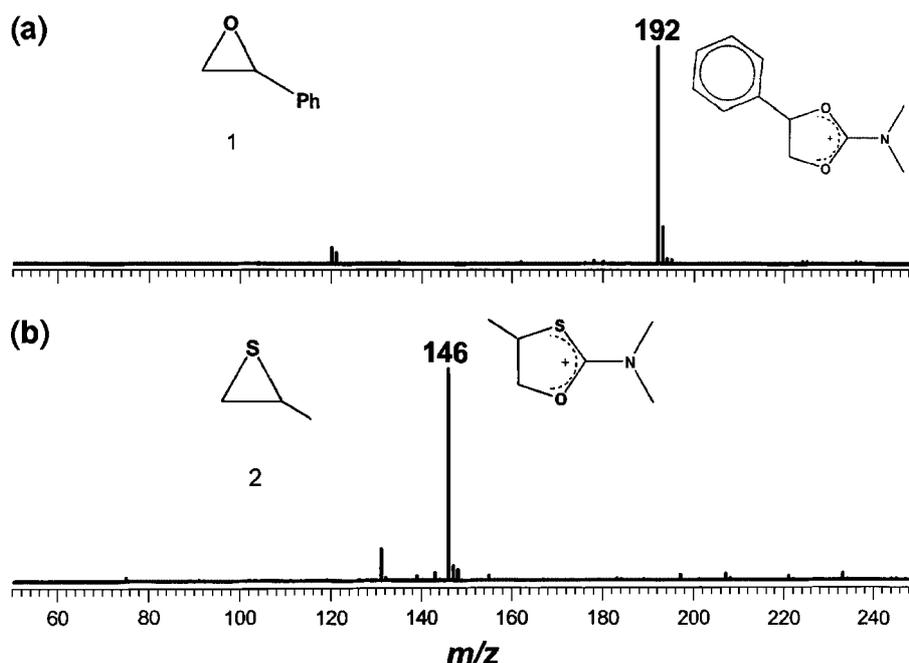


Figure 2. ESI-MS for methanolic solutions doped with TMU of (a) the epoxide **1**, and (b) the thio epoxide **2**. Note that the TMU-background ions (Fig. 1) were subtracted.

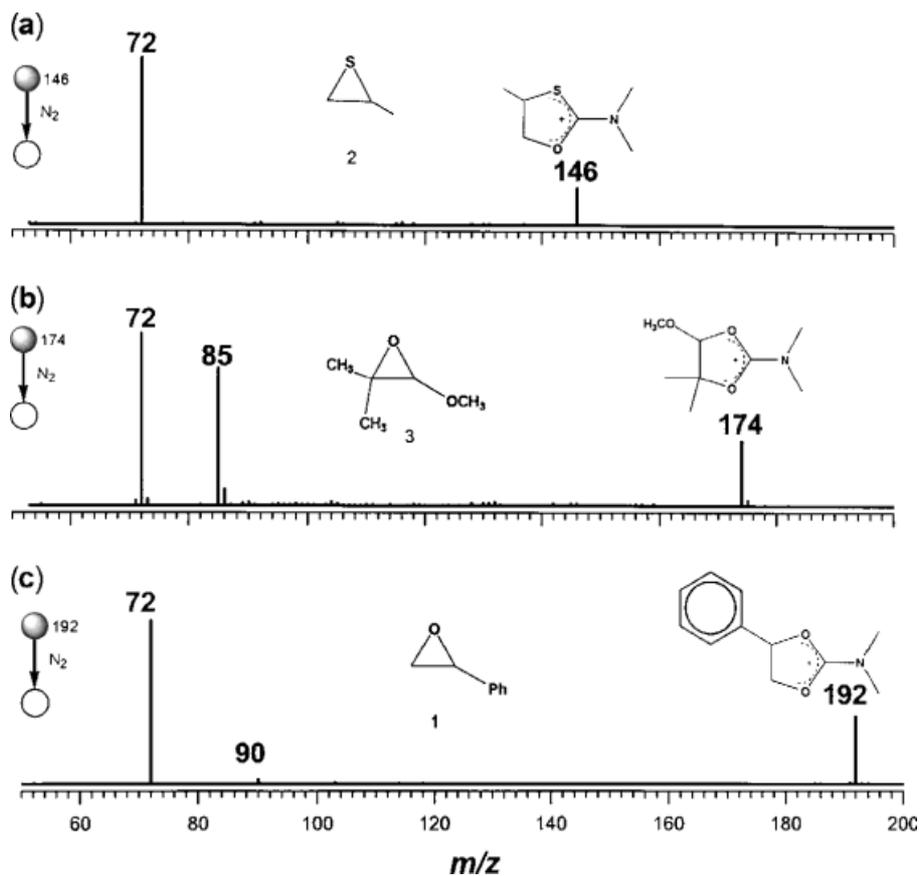


Figure 3. ESI-MS/MS for low-energy CID of the cyclic ionic acetals formed by the atmospheric pressure Meerwein reaction of the acylium ion $(\text{CH}_3)_2\text{NCO}^+$ with the (thio)epoxides (a) **2**, (b) **3**, and (c) **1**.

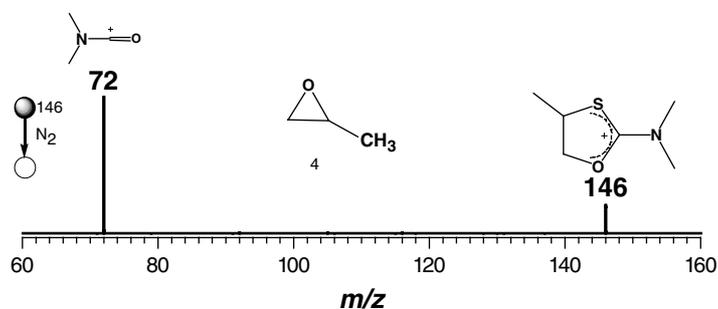
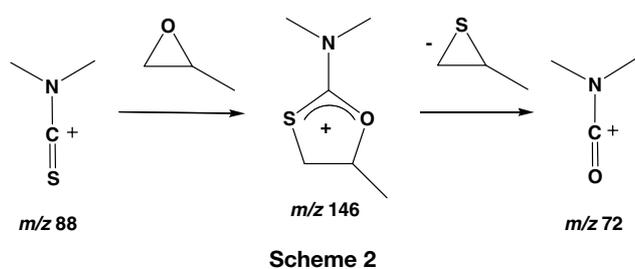


Figure 4. ESI-MS/MS for low-energy CID of the cyclic ionic thio acetal formed by atmospheric pressure Meerwein reaction of the (thio)acylium ion $(\text{CH}_3)_2\text{NC}=\text{S}^+$ with propylene oxide **4**. Note the nearly exclusive dissociation to the O-analog ion $(\text{CH}_3)_2\text{NCO}^+$, which points to the intermediacy of the cyclic Meerwein product.



(spectrum not shown). Figure 4 shows the ESI product ion mass spectrum of this Meerwein product. CID yields the O-analog acylium ion of m/z 72 as the exclusive fragment via an O/S replacement process (Scheme 2), which points

to intermediacy of a cyclic Meerwein product (compare to Fig. 3(a)).

Less volatile (thio)epoxides

After we verified that the atmospheric pressure Meerwein reaction indeed occurs with the volatile (thio)epoxides **1–4**, we tested this reaction for the heavier epoxides **5–7**.

When using TMU as the dopant, epoxides **5** and **7** readily and nearly exclusively form abundant Meerwein products (spectra not shown). The ESI-MS for **6** is particularly rich (Fig. 5) revealing a complex but structurally characteristic set of product ions. For illustration, the ESI-MS for **6** are shown with and without the background subtraction. As the spectrum in Fig. 5(a) shows, the acylium ion of m/z 72 reacts

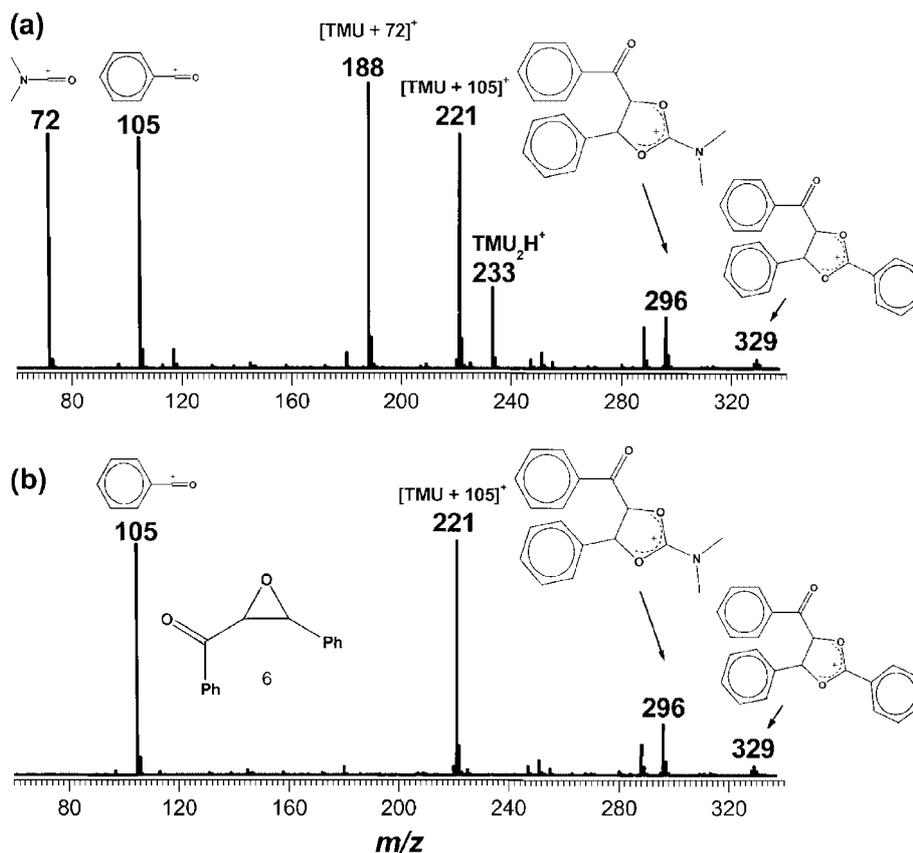
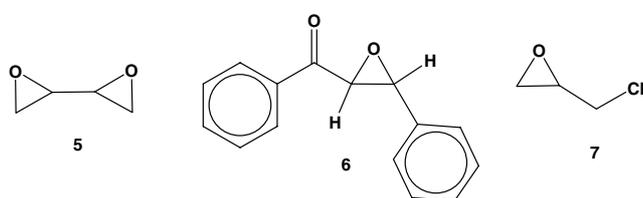


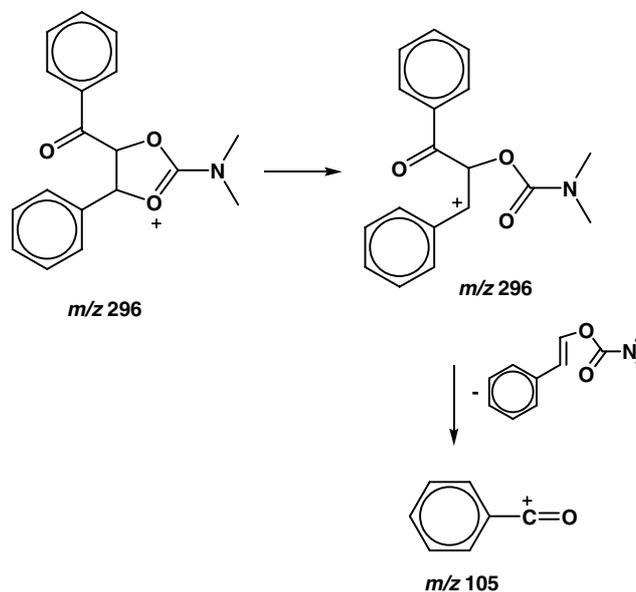
Figure 5. ESI-MS for a methanolic solution of **6** doped with TMU. For illustration, (a) shows the spectrum as measured, whereas (b) shows the spectrum after subtraction of the TMU-background ions.



competitively with both TMU and epoxide **6** to form $[\text{TMU} + \text{Ac}(72)]^+$ of m/z 188 and the Meerwein product of m/z 296. Another acylium ion, PhCO^+ of m/z 105, which likely arises from dissociation of the Meerwein product ion of m/z 296 (Scheme 3), acylates TMU to form $[\text{TMU} + \text{Ac}(105)]^+$ of m/z 221 while reacting with **6** to form a minor but detectable Meerwein product of m/z 329.

Further selectivity via CID experiments

Most Meerwein products dissociate mainly via low-energy collisions to re-form the reactant acylium ion (Fig. 4) or, for reactions with thio acylium ions, its O-analog (Fig. 2). As already pointed out, increased structural complexity along with the presence of other functional groups or substituents tend to favor competitive dissociations that can be useful for enhanced selectivity. The Meerwein product of m/z 296 from **6** (Fig. 6(a)) provides a clear example of this enhanced selectivity. This ion dissociates nearly exclusively not to form the reactant acylium ion $(\text{CH}_3)_2\text{NCO}^+$ of m/z 72, but to form instead and nearly exclusively the PhCO^+ acylium ion of m/z 105. A rationalization for this contrasting and ready



Scheme 3

dissociation may be assumed as due to charge stabilization by the phenyl substituent in the ring and the preference to form the highly resonance-stabilized PhCO^+ ion (Scheme 3).

Figure 6(b) and (c) show ESI-MS/MS for CID of the Meerwein products of epoxides **7** and **6**. These ions dissociate by the most common way to re-form the reactant acylium ion of m/z 72, but a second fragment of m/z 75 for **7** and of m/z 69 for **5** (*N,N*-dimethylcarbamic

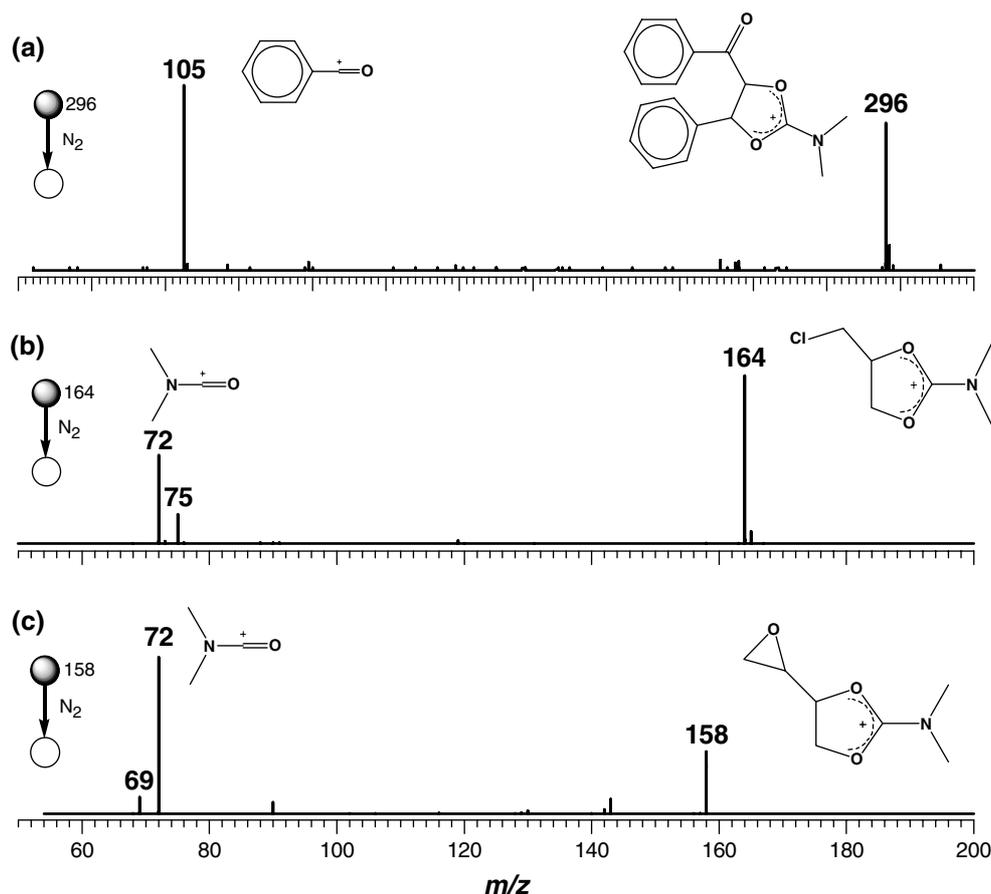


Figure 6. ESI-MS/MS for low-energy CID of the cyclic ionic acetals formed by the atmospheric pressure Meerwein reaction of the acylium ion $(\text{CH}_3)_2\text{NCO}^+$ with epoxides (a) **6**, (b) **7**, and (c) **5**.

acid loss) are also clearly detected.²² Similar results as those just discussed in detail for ESI were observed for APCI.

CONCLUSIONS

The gas-phase Meerwein reaction of (thio)acylium ions with (thio)epoxides can be efficiently performed under the atmospheric pressure conditions of both ESI and APCI. Therefore, the range of (thio)epoxides that can be reacted is greatly increased using these environment, which can now include less volatile compounds. Both tetramethylurea and tetramethylthiourea act as efficient dopants, and a variety of solvents can be used as demonstrated here with methanol and toluene. Enhanced selectivity in structural characterization or for the screening of cyclic acetals is gained by performing an on-line CID of Meerwein product ions, particularly for more structurally complex (thio)epoxides.

Acknowledgements

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