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International Journal of Mass Spectrometry 253 (2006) 281–287

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# Atmospheric pressure Eberlin transacetalization reactions in the heterogeneous liquid/gas phase

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Received 3 March 2006; received in revised form 1 May 2006; accepted 4 May 2006
Available online 16 June 2006

**Abstract**

The Eberlin reaction, the ionic transacetalization of cyclic acetals and analogues with acylium and related ions, is demonstrated in the course of ion/molecule reactions at atmospheric pressure. Selected gaseous acetals (1,3-dioxolane, 2-methyl-1,3-dioxolane, 2,2-dimethyl-1,3-dioxolane, 4-methyl-1,3-dioxolane, 2-phenyl-1,3-dioxolane, 1,3-dioxane, and 1,3,5-trioxane) react efficiently with the $(CH_3)_2NCO^+$ acylium ion, generated by electrosonic spray ionization (ESSI) of an aqueous/methanol solution of tetramethylurea (TMU), to furnish the characteristic cyclic ionic acetals, the Eberlin products, in moderate to high yields. It is proposed that acylium ions on the surface of the ESSI-generated droplets interact with gaseous neutral reagents. The Eberlin products dissociate exclusively to re-form the reactant $(CH_3)_2NCO^+$ acylium ion upon collision-induced dissociation (CID), confirming their structures. The intact adduct, i.e., acylium ion plus neutral reagent (the stable precursor of the Eberlin product), is observed in these experiments whereas it is not observed in studies of the same Eberlin reactions under conventional reduced pressure ion/molecule reaction conditions. It is suggested that under atmospheric pressure conditions these intact adducts are likely stabilized through deactivation via collision with buffer gas.

*Keywords:* Eberlin reaction; Ion/molecule reaction; Heterogeneous reaction; Atmospheric pressure reaction; Solvated ion

## 1. Introduction

Acylium ions, because of their relative ease of preparation, constitute a common and synthetically useful class of stable carbocations in the condensed phase. In the dilute gas-phase environment of the mass spectrometer, a variety of long-lived solvent- and counter-ion free acylium ions have been generated, isolated, and reacted, and a rich gas-phase chemistry has been observed for such gaseous ions. Among these reactions is the polar transacetalization, a reaction with neutral cyclic acetals now known as the Eberlin reaction, which occurs with acylium ions bearing both Lewis acidic and basic sites. The reaction occurs in the low-pressure environment of a mass spectrometer, to yield resonance-stabilized cyclic ionic acetals (Eberlin products) via the elimination of neutral aldehydes or ketones from the initial intact adducts [1]. The corresponding direct polar transacetalization of acylium ions is also known to occur in solution. For instance, solvated acylium ions formed from carboxylic acid chlorides in the presence of the strong Lewis acid antimony pentachloride, react with neutral 1,3-dioxanes to generate 1,3-dioxanium hexachloroantimonate salts in 25–95% yield [2].

Gas-phase ion chemistry under high-pressure conditions is of even greater relevance to solution phase chemistry than are conventional reduced pressure ion/molecule reactions. Two characteristics are of particular note [3–9]: (a) all chemical species encountered along the reaction coordinate are thermally equilibrated with the buffer gas, which allows the observed rate constant of ion/molecule reactions to be interpreted rigorously in terms of candidate mechanisms and potential energy surfaces for that reaction [4,10] and (b) the structural and stereochemical information derived from gas-phase ion chemistry under high pressure conditions, including atmospheric pressure, should

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doi:10.1016/j.ijms.2006.05.005

be more fully comparable with data from solution chemistry than low-pressure data, thus allowing meaningful correlations between gas-phase and condensed-phase ionic reactivity [6]. Recent examples of ion/molecule reactions carried out under atmospheric pressure conditions include the formation of TNT–Meisenheimer complexes from nitroaromatics [11], the interaction between piperidine and multiply-charged lysozyme ions generated by electrosonic spray ionization (ESSI) [12], and the oxidation of oleic acids by ozone occurring at charged-droplet surfaces [13].

It is also possible to use mass spectrometry to investigate solution-phase chemistry even more directly, by examining the reactions of solvated and microsolvated ions in the mass spectrometer. Partially solvated ions [14], including core hydroxide [15], acylium [16], halide [17], alkali metal [18], transition metal [19], and nucleic acid ions [20], have been generated and their behavior extensively studied [21]. Such ions, solvated with one or more molecules of water, alcohols, and other solvent species of organic and atmospheric interest, are relevant to solution chemistry. These newer studies provide information on ion solvation energy, as well as rate constants, isotope effects, and product distributions, as a function of the cluster size and composition, increasing our knowledge of solvation at the molecular level.

The Eberlin reaction has previously been reported to occur under in-source ion/molecule reaction conditions in an experiment in which tetramethylurea (TMU) was added to an acetal solution and then injected into the electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) source. Upon protonation, the basic TMU molecule dissociated to give the $(CH_3)_2NCO^+$ acylium ion which then reacted with the neutral acetal reagent to yield the corresponding Eberlin product [22] observed in the mass spectrum as the charged species. Meurer et al. interpreted their results on this system as involving the reactions of fully desolvated ions with neutral vapors of the acetal.

The study of Eberlin and coworkers [22] and the striking [1] similarity in the reactivity of acylium ions in the low pressure gas-phase environment and in the condensed phase, encouraged us to investigate the transacetalization Eberlin reaction of the solvated $(CH_3)_2NCO^+$ acylium ion under conditions where it could be established that the reacting ions were at atmospheric pressure. In doing this evidence was also sought on the point of whether the reacting ions were present in solution (droplets) or in the gas phase. We conclude that under the conditions used here, the reactions examined occur in the heterogeneous liquid/vapor phase, i.e., they involve the acylium ion in charged droplets and gaseous molecules of actals.

## 2. Experimental

All reagents were purchased from Sigma–Aldrich Inc. (Milwaukee, WI) and used with no further purification. The experiments were performed using a commercial LCQ ion trap mass spectrometer (Thermo Electron, San Jose, CA). The apparatus used to perform the experiments is shown in Fig. 1. The reactant ion $(CH_3)_2NCO^+$ was generated with a home-built ESSI ion source [23] similar to the commercial source from Prosolia Inc. (Indianapolis) by using a solution of TMU, 0.01 mol/L in methanol/$H_2O$ (1:1 by volume). To allow the formation of very small droplets and thus facilitate the reaction process, a low solution injection rate (3 μL/min) and a high nebulizer gas ($N_2$) pressure (150–200 psi) were used. The spray was directed towards the mass spectrometer inlet through a plastic tube (the reaction chamber, 10 mm ID and 40 mm length) containing vapors of the neutral reagents (evaporated from their neat liquids/solids in a cotton tip). These neutral reagents included 1,3-dioxolane, 2-methyl-1,3-dioxolane, 4-methyl-1,3-dioxolane, 2,2-dimethyl-1,3-dioxolane, 2-phenyl-1,3-dioxolane, 1,3-dioxane, 1,3,5-trioxane and 1,3-dithiane. The resulting products were monitored by the mass spectrometer, which was operated using the following parameters: (a) spray voltage 5 kV applied to the stainless steel needle of a 500 μL syringe; (b) capillary temperature 150 °C; (c) capillary voltage 44 V; (d) tube lens offset 55 V; (e) multipole 1 offset −8 V; (f) lens voltage −16 V; multipole 2 offset −10 V; (g) multipole RF amplitude 400 V. For the MS/MS experiments, the ion of interest was isolated using a mass-to-charge window width of 1 mass unit, and then dissociated via controlled collision with helium gas.

## 3. Results and discussion

In the Eberlin transacetalization reaction in the gas-phase environment, initial gas-phase *O*-acylation is followed by fast and thermodynamically favored ring opening and then recyclization with the release of the previously acetal-protected neutral carbonyl compound and the formation of the res-

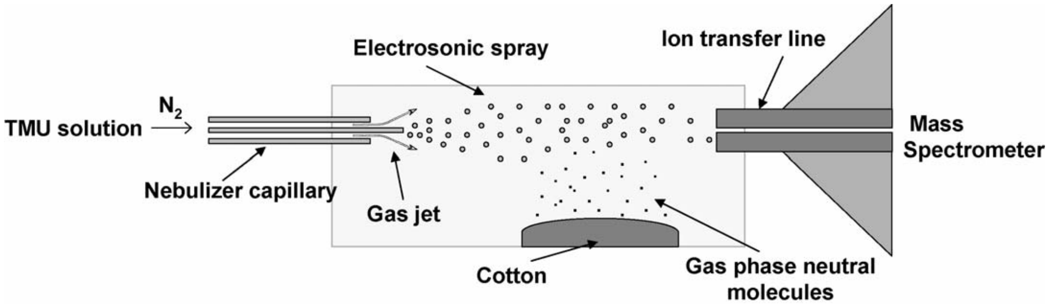


Fig. 1. Schematic of the apparatus used to perform the reactions.

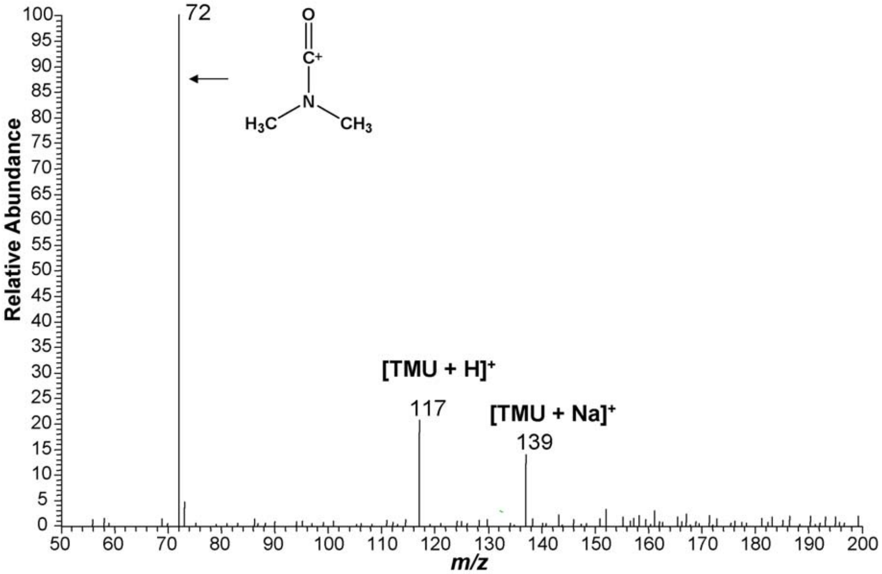


Fig. 2. ESSI(+) mass spectrum of tetramethylurea (TMU) in 1:1 water/methanol showing the presence of the $(CH_3)_2NCO^+$ acylium ion of *m/z* 72 and the protonated and sodiated TMU of *m/z* 117 and 139, respectively.

onance stabilized cyclic ionic acetal (the Eberlin product) [1].

Fig. 2 shows the ESSI(+) mass spectrum of a TMU solution in methanol/water. In addition to protonated and sodiated TMU (*m/z* 117 and 139, respectively), there is an abundant ion corresponding to the acylium ion $(CH_3)_2NCO^+$ at *m/z* 72. This ion is formed owing to the high lability of protonated TMU, which promptly dissociates by loss of a neutral molecule of dimethylamine (a metastable decomposition). The use of $(CH_3)_2NCO^+$ as reactant ion is highly convenient since it is the least acidic and the most reactive acylium ion so far tested in the gas-phase Eberlin transacetalization reactions [24–30]. The apparatus shown in Fig. 1 was employed to perform the reactions of solvated forms of this acylium ion: the neutral reactants (with simple structures and low molecular weights) were introduced in the reaction chamber and their vapors allowed to react with microdroplets containing the $(CH_3)_2NCO^+$ acylium ion generated under ESSI conditions. Table 1 summarizes the results. For each neutral reagent investigated, the mass-to-charge ratios and the relative abundances of the product ions as well as of the reactant acylium ion are shown. With a single exception (1,3-dithiane, for which an ionic transacetalization reaction was not observed), the ionic acetal (the Eberlin product) is the main reaction product. In the cases of 2-methyl-1,3-dioxolane, 4-methyl-1,3-dioxolane, 2,2-dimethyl-1,3-dioxolane and 1,3-dioxane, the Eberlin products were observed as the base peaks and the reaction yields (defined as the ratio of the intensity of the Eberlin product to those of total products) were over 60%. Fig. 3 shows, for instance, the ESSI(+) mass spectrum of the reaction between 4-methyl-1,3-dioxolane and the acylium ion. The abundant ion of *m/z* 130 is the Eberlin product (Scheme 1).

It is interesting to note that none of the protonated acetals were formed by the competitive and undesirable proton-transfer reaction since the highly basic TMU molecule preferentially retains the proton. Under high vacuum conditions however, protonated acetals as well as hydride abstraction products, are typically observed in the Eberlin reactions as competitive products [24–30] (the protonated acetals are likely to be formed via a secondary proton transfer process, for example, the reactions between the initial hydride abstraction products and the neutral acetals). This suggests that the acylium ion is present as the solvated species and not as the free gas-phase ion.

CID of the Eberlin products resulted in the re-formation of the $(CH_3)_2NCO^+$ acylium ion, an identical dissociation pattern with that observed for the fragmentation of the Eberlin transacetalization products formed under vacuum conditions

Table 1
Results from the heterogeneous atmospheric pressure reactions between the acylium ion $(CH_3)_2NCO^+$ of *m/z* 72 and the neutral reactants

| Neutral reactant | $(CH_3)_2NCO^+$ (relative intensity, %) | Eberlin product (*m/z*, relative intensity, %) | *O*-acylation adduct (*m/z*, relative intensity, %) |
|---|---|---|---|
| 1,3-Dioxolane | 100 | 116 (69) | 146 (18) |
| 4-Methyl-1,3-dioxolane | 14 | 130 (100) | 160 (43) |
| 2,2-Dimethyl-1,3-dioxolane | 10 | 116 (100) | 174 ([a]) |
| 2-Phenyl-1,3-dioxolane | 100 | 116 (15) | 226 ([a]) |
| 1,3-Dioxane | 25 | 130 (100) | 160 (5) |
| 1,3,5-Trioxane | 100 | 132 (36) | 162 ([a]) |
| 1,3-Dithiane | 100 | 146 ([a]) | 192 ([a]) |

[a] Not observed.

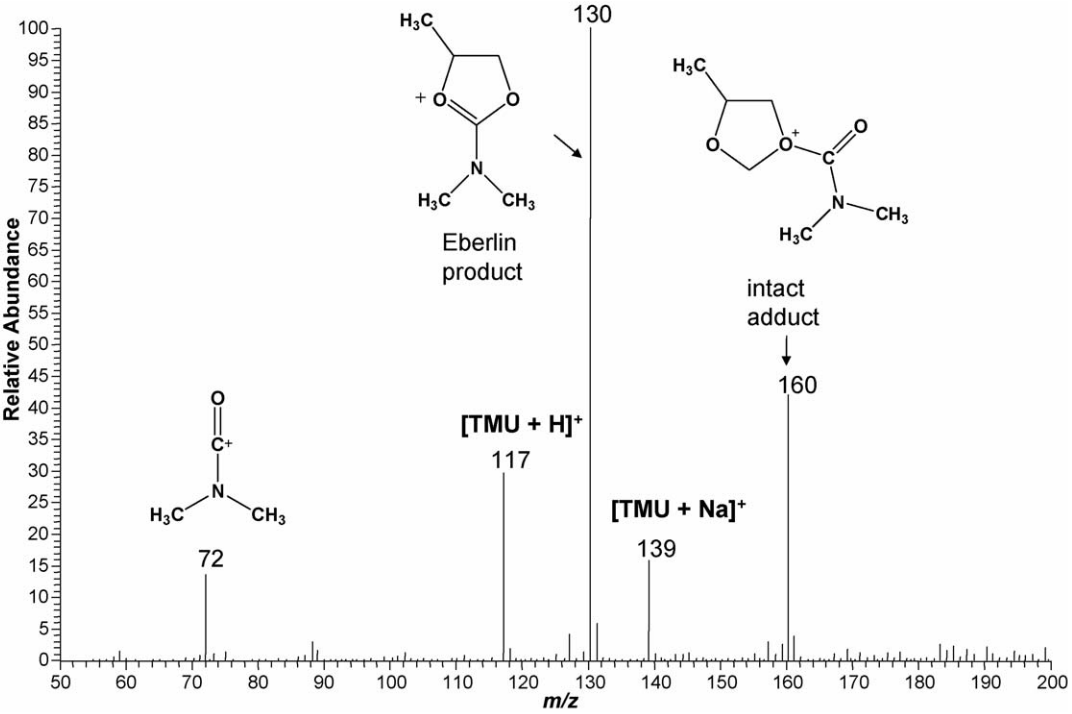
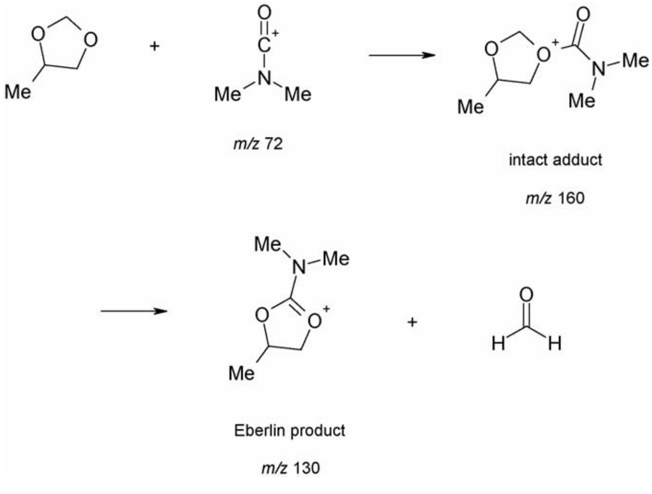


Fig. 3. Mass spectrum displaying the result of the reaction between the $(CH_3)_2NCO^+$ acylium ion of *m*/*z* 72 and 4-methyl-1,3-dioxolane conducted at atmospheric pressure.

[24–30]. For instance, Fig. 4 shows the CID mass spectrum of the Eberlin product of *m*/*z* 130, formed in the reaction between $(CH_3)_2NCO^+$ of *m*/*z* 72 and 4-methyl-1,3-dioxolane, which fragments back to reconstitute the acylium ion.

In this reaction, another product of *m*/*z* 160 was observed (Fig. 3 and Table 1) and it is ascribed to the intact adduct between the $(CH_3)_2NCO^+$ acylium ion and 4-methyl-1,3-dioxolane, which is the precursor of the more stable Eberlin product (Scheme 1). As expected, CID of this intact adduct generated both the Eberlin product and the acylium ion of *m*/*z* 72 (Fig. 5). Similar intact adducts were also observed in the reactions of the $(CH_3)_2NCO^+$ acylium ion with 1,3-dioxolane (*m*/*z* 146) and 1,3-dioxane (*m*/*z* 160) and their fragmentation by CID (spectra not shown) furnished the corresponding Eberlin products (*m*/*z* 116 and 130, respectively) as well as the original acylium ion. This result is in agreement with the proposed Eberlin reaction mechanism and it suggests that the mechanism elucidated for isolated ions in the gas phase also applies to the solution phase reaction (as previously suggested) and to the reaction in the heterogeneous solvent/vapor phase examined here.



Scheme 1.

Despite the fact that the prototype Eberlin reaction (and its variants) has been extensively studied throughout the last decade, mainly under conventional high-vacuum conditions, only a few examples show the detection of such intact adducts. For instance, we previously observed the formation of a low-intensity adduct of *m*/*z* 194 upon the interaction between the mass-selected phenylnitrenium ion ($PhNH^+$, *m*/*z* 92) and the gaseous 2,2-dimethyl-1,3-dioxolane. It was suggested that this adduct subsequently rearranges to form the expected Eberlin product, i.e., the protonated *N*-heterocycle benzomorpholine [31]. Under the atmospheric pressure conditions employed in the present study, the intact adduct is deactivated via successive collisions with surrounding molecules and is readily detected in competition with conversion to products. Previously it was also reported that chemical ionization (CI) of dioxolanes using acetone (i.e., acylium ions as the reagent ions), produced the intact adduct. The CI study (ca. 0.5 torr) along with the present result at atmospheric pressure, strongly supports the argument that adduct ions are stabilized by collision at higher pressures.

Table 1 also shows that 1,3-dithiane, the sulfur analog of 1,3-dioxane, does not yield the corresponding Eberlin adduct, a result consistent with the data from previous reactions conducted under high-vacuum conditions [27,30,32–34]. Interestingly, the cyclic acetal 1,3,5-trioxane, a trimer form of formaldehyde in

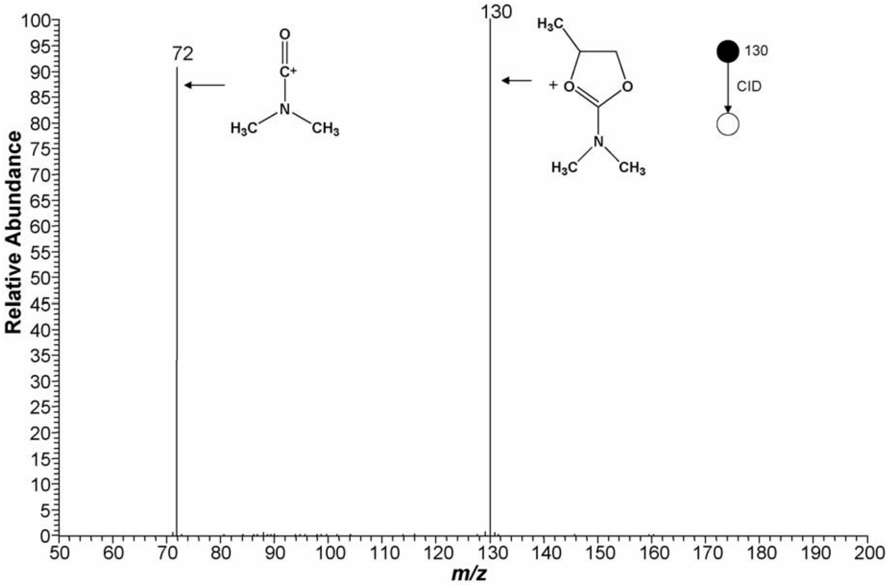


Fig. 4. Double-stage MS$^2$ mass spectrum showing CID of the Eberlin product of *m*/*z* 130 formed in the reaction between the $(CH_3)_2NCO^+$ acylium ion of *m*/*z* 72 with 4-methyl-1,3-dioxolane conducted at atmospheric pressure.

which three oxygen atoms are evenly distributed through the six-member ring [35] produced moderate yields of the Eberlin product (Scheme 2). The reaction was unsuccessful when conducted under high-vacuum conditions, due to the rapid irreversible decomposition of 1,3,5-trioxane to formaldehyde during the ultrafast heating required for vaporization.

The atmospheric pressure ionic transacetalization reaction is suggested to occur via the interaction of solvated $(CH_3)_2NCO^+$ acylium ion (in the liquid phase, viz. in the charged ESSI-generated droplets) with the neutral reagents (in the gas phase). Evidence for this has already been provided, including the lack of proton transfer which would be expected in the case of unsolvated ions. Since the usual procedures for solvent removal (heating and countercurrent gas flow) were not used, the ESSI-generated droplets are not completely evaporated during crossing of the short reaction chamber. Furthermore, these ESSI-generated droplets likely contain high concentrations of the reactive $(CH_3)_2NCO^+$ acylium ion, as judged by the presence of an intense peak of *m*/*z* 72 in the ESSI mass spectrum of the aqueous/methanol solution of TMU (Fig. 2). Thus, it is reasonable to argue that the polar acetal molecules are collected from the gas phase by the charged droplets and react with the acylium ions distributed at the liquid surface, where the intact adduct is formed and irreversibly converted to the more stable

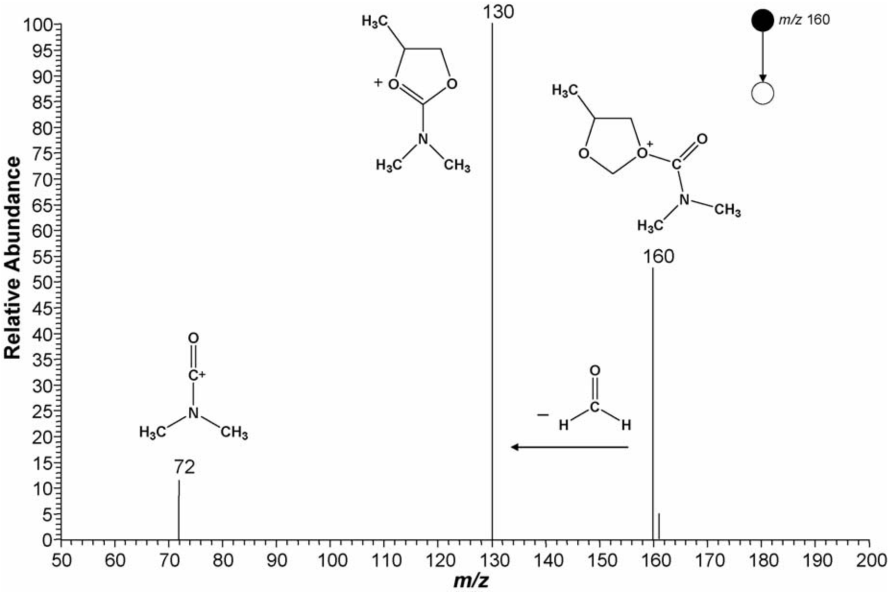
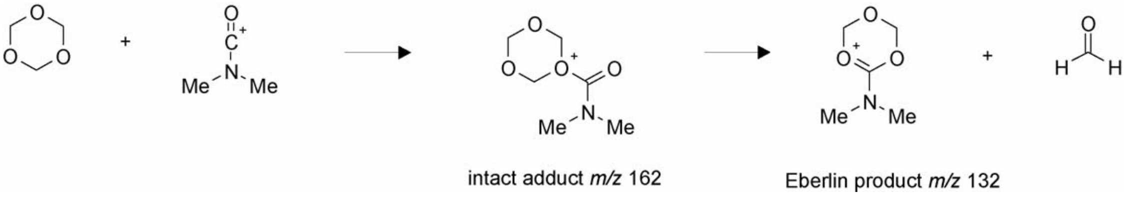


Fig. 5. Double-stage MS$^2$ mass spectrum showing CID of the intact adduct of *m*/*z* 160 formed in the reaction between $(CH_3)_2NCO^+$ acylium ion of *m*/*z* 72 and 4-methyl 1,3-dioxolane.



Scheme 2.

Eberlin product. It should be mentioned that similar experiments were performed by Fenn who used the ability of charged liquid droplets to collect polar trace species from ambient air as a method of air sampling based on electrospray [36].

Additional evidence for the heterogeneous-phase character of the reaction was obtained by removing any solvent-free acylium ions present in the plume of the ESSI spray using a deflecting electric field established between two parallel stainless steel plates, 2 cm apart [37]. This “ion switch” was first placed in between the ESSI ion source and the atmospheric pressure sampling inlet of the mass spectrometer. When a potential of 1000–3000 V was applied between the two plates, the total ion signal decreased, indicating deflection of the desolvated gas-phase ions. The remaining signal must be due to the heavier droplets. The reaction chamber was then placed between these two metallic plates and the reaction was conducted, in the presence and absence of the electric field. Both experiments showed essentially the same results (the formation of the Eberlin product ions), thus suggesting that the occurrence of the Eberlin reactions in this study is predominantly the result of interaction between acylium ions in the liquid phase (droplet) and gaseous acetal neutrals on the droplets surface.

## 4. Conclusions

We have described some examples of the Eberlin reaction conducted under atmospheric pressure conditions but using solvated ions. Acylium ions, generated via ESSI of an aqueous solution of TMU, react efficiently with gaseous cyclic acetals to yield the corresponding ionic transacetalization products. It is suggested that the initial intact adducts are formed on the surface of the ESSI droplets and that they are subsequently converted to the more stable Eberlin products, just as happens in solution. Under these conditions the competitive proton transfer process was not observed due to solvation of the reactant acylium ion of $m/z$ 72. The insignificant effect of an external electric field applied to the reaction chamber also suggests that the occurrence of the Eberlin reactions under these conditions is due to solvated acylium ions in the droplets. Under different conditions, including in source conditions using ESI as well as conventional ion/molecule reaction conditions, the reaction involves fully desolvated gas-phase ions. Prospectively, biological applications of the present study are possible since peptides and proteins contain many carbonyl functional groups which could serve as precursors of acylium ions and undergo Eberlin reactions. When combined with previous studies of Eberlin reactions in vacuum and in solution, the data presented here clearly show that the reaction can occur across different media from low-pressure gas phase, through high-pressure gas phase to solution. This makes it a prime target for further studies aimed at elucidating the effects of medium on reactivity, including more quantitative studies of reaction rates.

## Acknowledgements

The authors acknowledge financial support from National Science Foundation, Grant CHE04-12782, the US Department of Energy and the Office of Basic Energy Sciences. R.A. and L.S.E. also acknowledge the Brazilian National Research Council (CNPq) for research fellowships.

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