

JMS Letters

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Dear Sir,

Ambient Eberlin reactions via desorption electrospray ionization mass spectrometry

Mass spectrometry has become an essential technique in many branches of science. Its very broad range of applications results mainly from the introduction of a powerful set of techniques that have revolutionized the ionization process, which is the *sine qua non* condition for MS analysis. Recently, Cooks *et al.*^{1–3} introduced a new ionization technique: desorption electrospray ionization (DESI). This innovative approach allows the direct *in situ* ionization of chemicals placed on surfaces under ambient conditions. For DESI, the surface containing the analyte is exposed to electrosprayed charged droplets carried in a very high-velocity gas stream. The analyte is ionized and desorbed into the gas phase and then transferred to the mass spectrometer by electrostatic and pneumatic means.⁴ Several applications of DESI-MS have now appeared, such as its use in direct examination of biological tissues,⁵ on-spot MS analysis⁶ for thin-layer chromatography⁷ and trace level ambient detection of explosives.⁸

In vacuo ion/molecule reactions, that is, those performed in the low pressure, very dilute environment of the mass spectrometer, are powerful tools in chemistry since they provide access to key properties and intrinsic reactivities of a great variety of solvent- and

counterion-free gaseous ions.^{9–12} These gas-phase reactions also offer an elegant approach to determine the structures of isolated ions and neutral molecules, and an arsenal of class-selective and/or structurally diagnostic reactions is available.^{13,14} Recently, we showed that ion/molecule reactions can be conveniently performed under the atmospheric pressure conditions of both electrospray ionization and atmospheric pressure chemical ionization.¹⁵ We first demonstrated this principle for the Eberlin reaction (polar transacetalizations of acylium ions with cyclic acetals),^{16,17} and then for Meerwein reactions of acylium ions with epoxides and thioepoxides.¹⁸ Herein, we report that *ambient* Eberlin reactions can also be efficiently performed under the atmospheric pressure environment of DESI.¹⁹

The cyclic acetals 1–5, used as proof-of-principle analytes, were deposited in a paper target surface (1 ml of a 10^{-3} M l^{-1} solution in methanol) and sprayed with an acidified water:methanol 1:1 solution (10^{-3} M l^{-1}) of tetramethyl urea (TMU). Care should be taken when selecting DESI solvents as they may react with the acylium ion as is, for instance, the case with nitriles.²⁰ Under DESI conditions (see below), the gaseous acylium ion $(CH_3)_2NCO^+$ is produced from self-dissociation of the labile $[TMU + H]^+$ species. The gaseous $(CH_3)_2NCO^+$ ion (the most reactive acylium ion so far tested in Eberlin reactions)²¹ reacts with the neutral acetal placed on the surface, and the products of the reaction (Fig. 1) are clearly detected and characterized via single (MS) and double-stage (MS^2) mass spectrometric experiments performed with a tandem Q-Trap (Applied Biosystems do Brasil, São Paulo, SP) mass spectrometer. Although the Q-Trap ESI source is not a source optimized for DESI, we tried to reproduce DESI conditions^{1–3} as closely as possible, while trying to maximize product yields for the Eberlin reaction.

Figure 2 shows, as an example, the DESI-MS for an equimolar mixture of cyclic acetals 1 and 4. Note the detection of the main

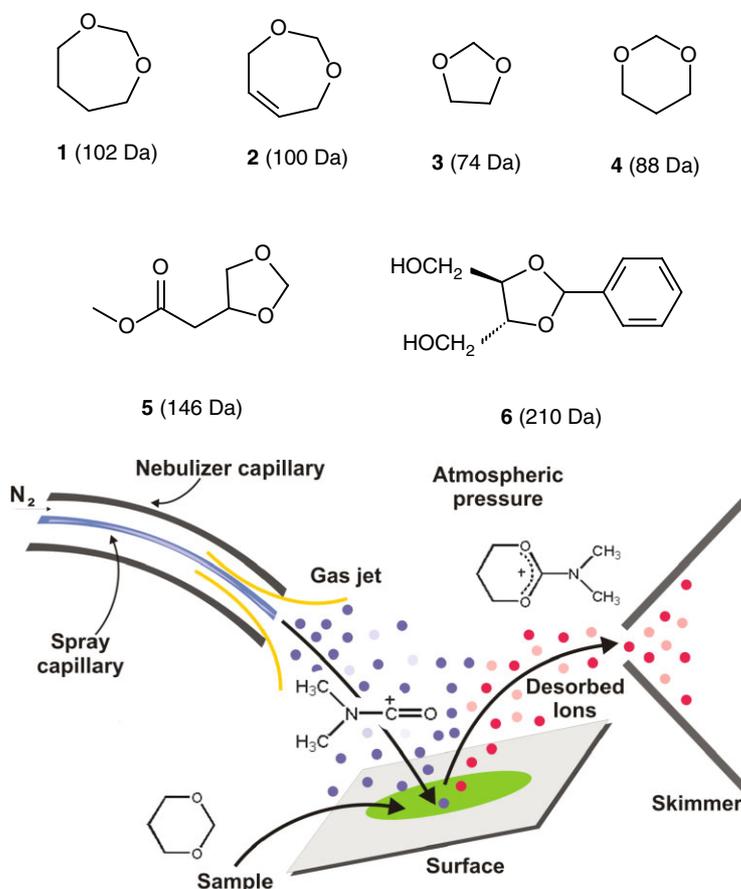


Figure 1. Schematic representation of *ambient* Eberlin reactions under DESI.

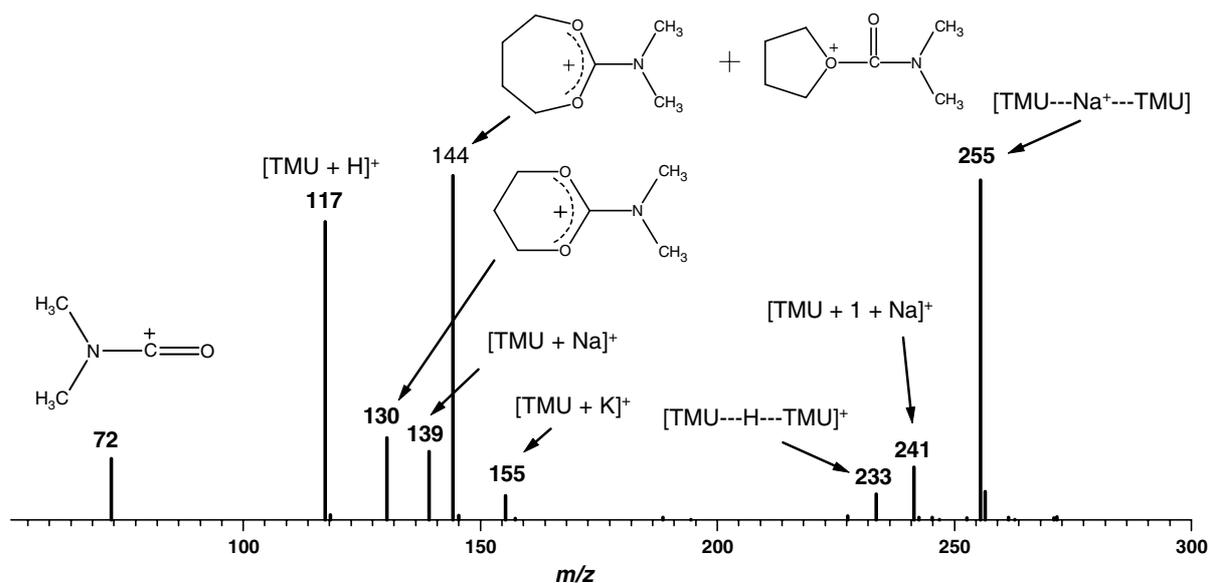


Figure 2. DESI-MS for *ambient* Eberlin reactions of a mixture of cyclic acetals **1** and **4** acquired by electrospraying a paper surface with an acidified water : methanol solution of TMU. The experiment was performed using the standard ESI source of a Q-Trap mass spectrometer with the following major operating conditions: 15 $\mu\text{l min}^{-1}$ flow rate, nebulizer gas temperature of 350 $^{\circ}\text{C}$ and backpressure of 40 psi, and needle voltage of 5500 V. Note that blank-spectrum subtraction yields a rather clean DESI spectrum (not shown) in which the ions of m/z 130 and 144 are of high relative abundance.

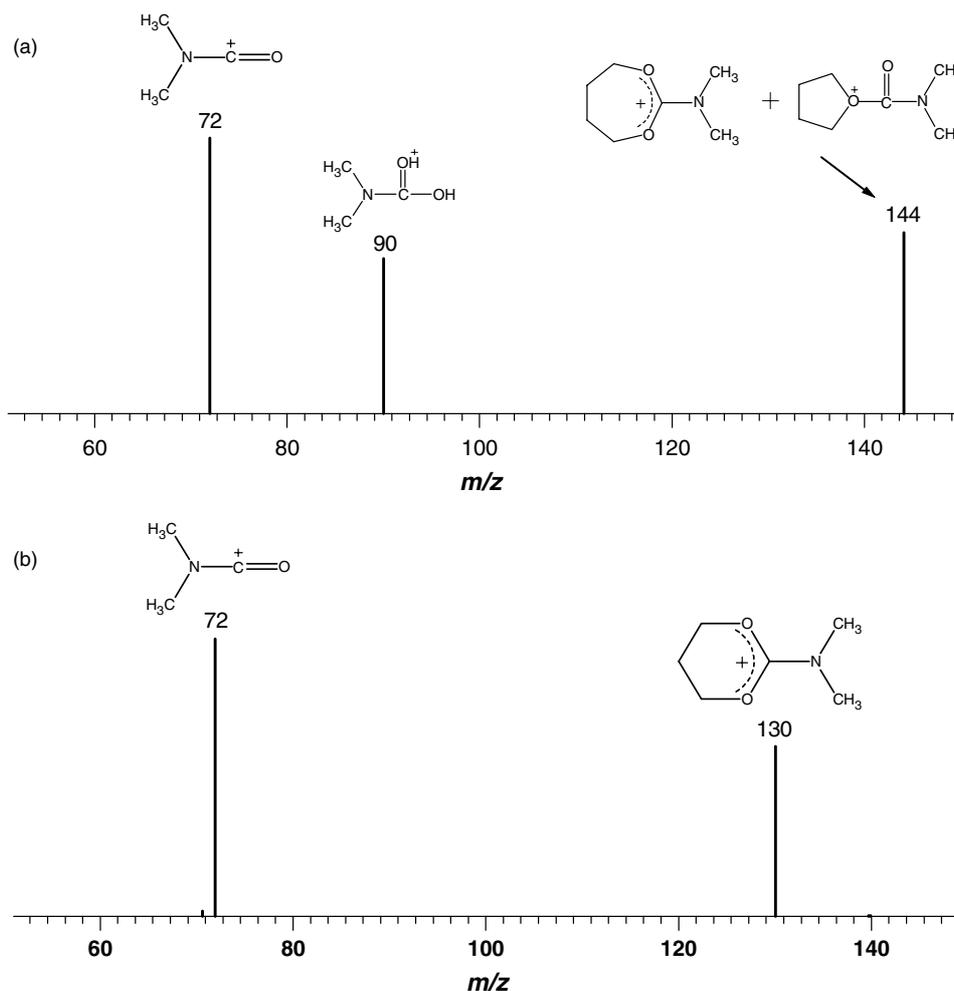


Figure 3. DESI-MS/MS for CID of the product ions of (a) m/z 144 and (b) m/z 130 formed via *ambient* Eberlin reactions of $(\text{CH}_3)_2\text{NCO}^+$ with the cyclic acetals **1** and **4**.

reactant ion, that is, the acylium ion $(\text{CH}_3)_2\text{NCO}^+$ of m/z 72, as well as its precursor $[\text{TMU} + \text{H}]^+$ of m/z 117 and the TMU proton-bound dimer $[\text{TMU}-\text{H}-\text{TMU}]^+$ of m/z 233. Interestingly, $[\text{TMU} + \text{Na}]^+$ of m/z 139 and $[\text{TMU}-\text{Na}-\text{TMU}]^+$ of m/z 255 as well as $[\text{TMU} + \text{K}]^+$

of m/z 155 were not detected by ESI-MS in the TMU solution, so they appear to arise from Na^+ and K^+ picked up from the paper surface. Besides these common ions, product ions of m/z 130 and 144 arising from ambient Eberlin reactions are also clearly detected. In fact, it

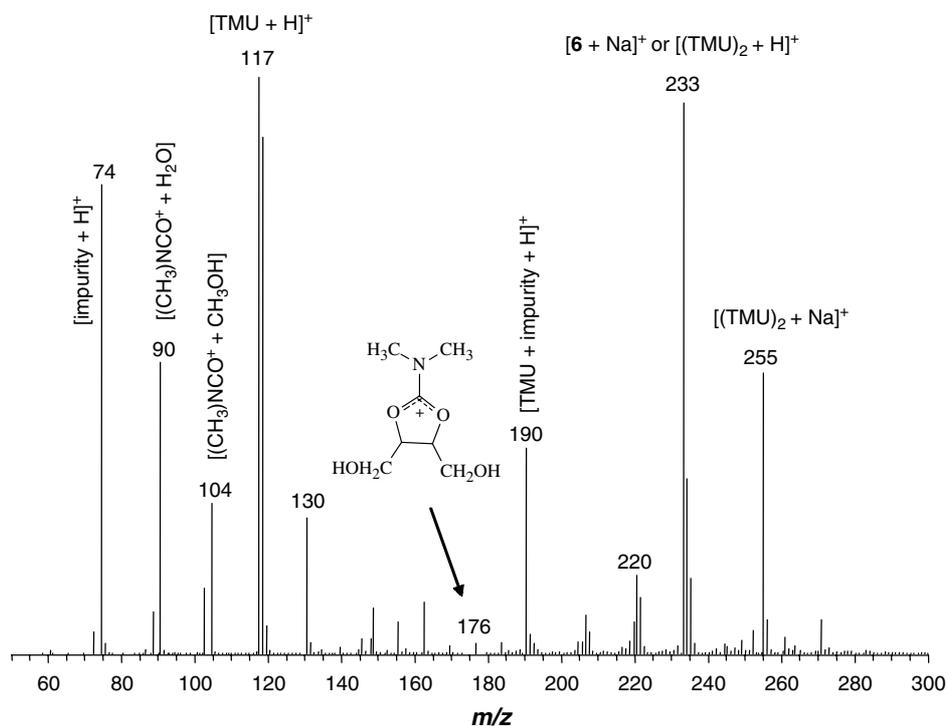


Figure 4. DESI-MS for *on-surface* Eberlin reactions of cyclic acetals **1** and **4** acquired by electrospraying a paper surface with an acidified water : methanol solution of TMU. The ions of m/z 74 and 190 are due to an unknown background impurity. The experiment was performed using a DESI source (Prosolia) coupled to a LTQ mass spectrometer (ThermoElectron). Typical operating conditions were as follows: spray voltage of 5 kV applied to the stainless steel needle of a 500 μl syringe; capillary temperature of 150 $^\circ\text{C}$ and capillary voltage of 44 V, tube lens offset 55 V, multipole 1 offset of -8 V, lens voltage of -16 V, multipole 2 offset of -10 V and multipole RF amplitude of 400 V. Note that blank-spectrum subtraction yields a rather clean DESI spectrum (not shown) in which the ion of m/z 176 is of high relative abundance.

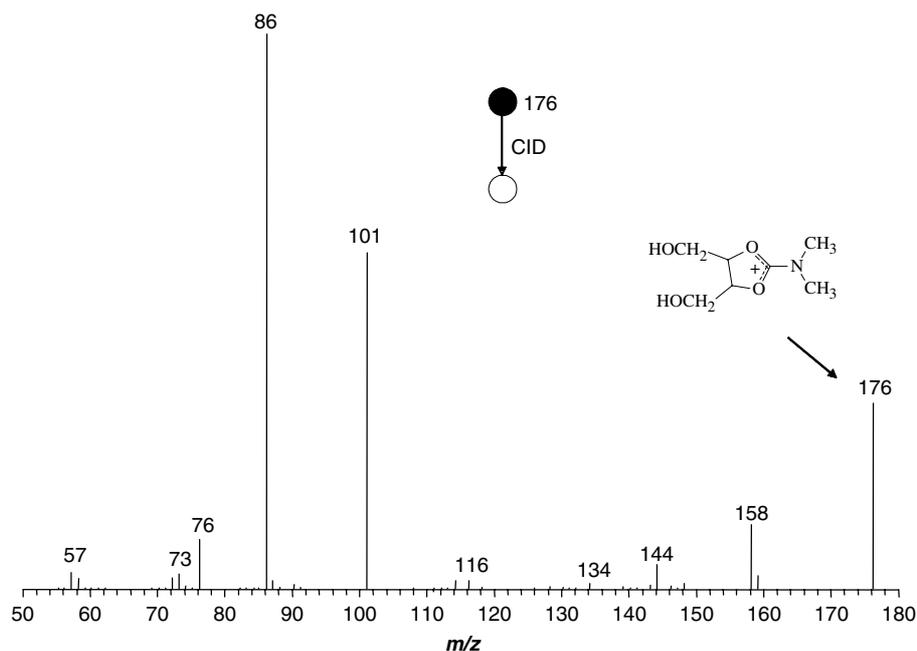
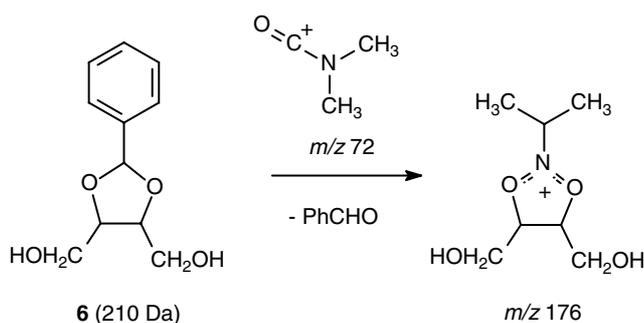


Figure 5. DESI-MS/MS for CID of the product ion of m/z 176 formed via *on-surface* Eberlin reaction of $(\text{CH}_3)_2\text{NCO}^+$ with the cyclic acetal **6**.



Scheme 1. Eberlin product of m/z 176 formed via on-surface reaction of $(\text{CH}_3)_2\text{NCO}^+$ with the cyclic acetal **6**.

is to be noted that the seven-membered cyclic acetal **1** is known to produce a mixture of the Eberlin transacetalization product and a seven-to-five ring contraction product.²² The other cyclic acetals **2** (m/z 142), **3** (m/z 116) and **5** (m/z 188) were also found to form the corresponding Eberlin products under similar DESI conditions (spectra not shown).

To investigate whether *ambient* Eberlin reactions indeed occur in a heterolytic fashion under DESI, the corresponding product ions were selected and subjected to collision-induced dissociation (CID). As Fig. 3 illustrates for the Eberlin products of **1** and **4**, identical dissociation patterns to those observed for the products formed by *in vacuo* Eberlin reactions²⁰ were observed. That is, the ion of m/z 144 (actually a mixture of the Eberlin product and a ring-contraction product from **1**)²² dissociates to form two major fragment ions: protonated dimethyl carbamic acid of m/z 90 and the reactant acylium ion of m/z 72. The ion of m/z 130 (from **4**) dissociates exclusively to the acylium ion of m/z 72.^{16,17}

To verify whether Eberlin reactions indeed occur mainly due to analyte pick up promoted by the charged droplets, and not predominantly *in vacuo* somewhere inside the mass spectrometer as a result of simple acetal evaporation, the much less volatile and polar acetal (+)-2,3-*O*-benzylidene- D -threitol **6** (b.p. of 381 °C) was also tested. Reaction with **6** was conducted using an optimized DESI source (Prosolia, Indianapolis, IN) coupled to a LTQ mass spectrometer (ThermoElectron, CA). For the DESI-MS/MS experiments, the ion of interest was isolated using an m/z window width of 1 unit, and then dissociated via controlled collision with helium gas.

Figure 4 shows the DESI-MS for such a reaction. Besides the abundant ions of m/z 117, 233, and 255, the Eberlin product of m/z 176 (Scheme 1) is also observed. Note in Fig. 4 that the 'naked' acylium ion $(\text{CH}_3)_2\text{NCO}^+$ of m/z 72 is barely detected by contrast to what is seen in the DESI-MS of Fig. 2. Under the DESI conditions used in the Prosolia source, solvated forms of the acylium ion were the most abundant species, that is, $[(\text{CH}_3)_2\text{NCO} + \text{H}_2\text{O}]^+$ of m/z 90 and $[(\text{CH}_3)_2\text{NCO} + \text{CH}_3\text{OH}]^+$ of m/z 104. This result indicates therefore that, as for the 'naked' ion (Fig. 2), solvated $(\text{CH}_3)_2\text{NCO}^+$ ions are also able to promote *ambient* Eberlin reactions under DESI conditions. Note also that although the Eberlin product ions were detected as low-abundance ions in the 'rough' spectra of Figs 2 and 4, proper blank-spectrum subtraction removes most of the ions related to precursors, reactant ion and impurities yielding much cleaner DESI mass spectra (not shown) in which the Eberlin product ions are of high relative abundances.

The selection and CID of the product ion of m/z 176 (Fig. 5) shows that it displays dissociation chemistry very different from that commonly observed for Eberlin product ions (the re-forming of the reactant acylium ion,¹⁹ in this case $(\text{CH}_3)_2\text{NCO}^+$ of m/z 72). This contrasting behavior is probably promoted by the hydroxymethylene C3 and C4 groups.²³ Although some fragment ions are easily assigned, such as those from loss of H_2O (m/z 158) and CH_3OH (m/z 144), there may exist different routes to the major fragment ions of m/z 101 and 86. An investigation on the dissociation chemistry of this ion is underway in our laboratory.

We have therefore demonstrated, using *on-surface* Eberlin reactions of cyclic acetals with acylium ions as an example, that class-selective or structurally diagnostic reactions^{16,17} can be performed under DESI-MS conditions. Once fully optimized (we are currently evaluating the use of solutions of acylium ion salts for increasing yields), DESI-MS should provide a highly suitable environment

in which to perform ion/molecule reactions capable of providing fine structural information for molecules now placed on different surfaces under ambient condition.

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Yours,

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