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Ionic Transacetalization with Acylium Ions: A Class-Selective and Structurally Diagnostic Reaction for Cyclic Acetals Performed under Unique Electrospray and Atmospheric Pressure Chemical Ionization In-Source Ion−Molecule Reaction Conditions

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Ionic transacetalization of cyclic acetals with the gaseous $(CH_3)_2NCO^+$ acylium ion has been performed under unique in-source ion−molecule reaction (in-source IMR) conditions of electrospray (ESI) and atmospheric pressure chemical ionization (APCI). In-source IMR under ESI and APCI greatly expands the range of neutral molecules that can be brought to the gas phase to react by ionic transacetalization, a general, class-selective and structurally diagnostic reaction for cyclic acetals (Moraes, L. A. B.; Gozzo, F. C.; Vainiotalo, P.; Eberlin, M. N. *J. Org. Chem.* 1997, *62*, 5096). Heavier, more polar, and less volatile cyclic acetals than those previously employed in quadrupole collision cells are shown to react efficiently by ionic transacetalization under the ESI and APCI in-source IMR conditions. Tetramethylurea (TMU) acts as an efficient dopant, being co-injected with the acetal in either benzene, toluene, methanol, or water/methanol solutions. Under APCI or ESI, the basic TMU dopant is protonated preferentially, and the labile protonated TMU then undergoes dissociation to $(CH_3)_2NCO^+$, the least acidic and the most transacetalization-reactive acylium ion so far tested. Under the relatively high-pressure, low-energy collision conditions set to favor associative reactions, $(CH_3)_2NCO^+$ reacts competitively both with TMU to form acylated TMU and with the acetal via ionic transacetalization to form the respective cyclic ionic acetals. Spectrum subtraction removes the ionic products of the dopant (TMU) self-reactions, thus providing clean ion−molecule reaction product ion mass spectra, which are used for the selective, structurally diagnostic detection of cyclic acetals. Information on ring substituents comes from characteristic mass shifts resulting from aldehyde/ketone by acylium ion replacement. Enhanced selectivity in structural characterization or chemical recognition for cyclic acetal monitoring is gained by performing on-line collision-induced dissociation via tandem mass spectrometric experiments. Most cyclic ionic acetals dissociate exclusively or nearly exclusively to re-form the reactant $(CH_3)_2NCO^+$ acylium ion whereas the presence of additional functional groups with increased structural complexity tends to favor other specific but likewise selective dissociation channels.

Ionization techniques performed under atmospheric pressure: atmospheric pressure chemical ionization (APCI),[1] atmospheric pressure photon ionization,[2] and atmospheric pressure electrospray ionization (ESI)[3] along with matrix-assisted laser desorption ionization[4] have revolutionized the way molecules are ionized and transferred to the gas-phase environment of mass spectrometers for mass analysis, structural characterization, and physicochemical property measurements.[5] API techniques have greatly expanded the range of molecules that can be ionized for MS analysis by including those of much greater polarity,[6] molecular complexity,[7] and higher mass, now up to millions of mass units,[8] so much so that exceptions of condensed matter constitu-

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ents that cannot be brought to the gas phase in an ionized form for MS investigation are becoming rare.

API techniques are soft as they produce "room-temperature", relatively cold molecules in either their protonated, MH^+, cationized, MX^+ (X = metal), or deprotonated, $[M - H]^+$, forms. Exclusively or nearly exclusively formation of these "intact" (or nearly intact) and stable ionized molecules is a great advantage for molecular mass measurements and mixture analysis. But the lack of dissociation eliminates the structural information provided by the lighter, subunit ionic fragments. Such a limitation can be conveniently solved, however, by on-line collision-induced dissociation (CID) performed via tandem mass spectrometric experiments. Interestingly, the high atmospheric pressure environment of API techniques also opens the unique opportunity to perform efficient in-source dissociation of the intact MH^+, MX^+, or $[M - H]^-$ ions. In-source CID[9] is a less refined technique than tandem CID as no mass selection of the parent ion occurs but the in-source alternative has the advantage of being available in "MS-only" mass spectrometers by simply increasing the kinetic energy of the parent ions during their in-source trajectory.

Although both ionization-induced dissociation and CID are very powerful in revealing structural characteristics (atom connectivities) of gaseous ions, and are used as the standard MS method of structural molecular analysis,[10] class-selective and structurally diagnostic ion−molecule reactions performed either under chemical ionization conditions or via more refined well-controlled tandem mass spectrometric experiments with mass-selected ions[11] are also powerful for structural elucidation as chemical reactions rather than bonding breaking processes are used to reveal the structural characteristics of the reactant ion. Such reactions can be designed to reveal fine structural details as they are sensitive to electronic and steric effects and to geometric details such as presence and relative position of functional groups, molecular configuration and conformation.[12]

Additionally, the gas-phase environment of the mass spectrometer with the diversity of MS ionization techniques opens straightforward access to a great variety of ions of many classes. For instance, acylium ions ($R-C^+=O$) are very common and highly stable gaseous ions, and as their neutral counterparts, the carbonyl compounds ($RR_1C=O$), they have been found by MS techniques to display a rich, very diverse gas-phase reactivity.[13] Among the many gas-phase acylium ion reactions, ionic transacetalization with neutral cyclic acetals (the Eberlin reaction)[14] is quite general and has found a variety of applications for functional group screening and fine structural characterization of ions and neutrals.[15] To perform such reactions under well-controlled, refined tandem mass spectrometric conditions using mass-selected acylium ions, the neutral acetals must, however, be sufficiently volatile so as to fulfill properly the collision cell region.[14,15] Failure to display the proper volatility for many neutral acetals has been a major limitation for a more general application of this class-selective and structurally diagnostic ion−molecule reaction.

Herein we describe the use of unique MS in-source ion−molecule reaction *(*in-source IMR) conditions for ESI and APCI using tetramethylurea (TMU) as an efficient dopant to perform class-selective and structurally diagnostic ionic transacetalization of the gaseous acylium ion, $(CH_3)_2NCO^+$, with a variety of relatively polar, heavy, and structurally complex cyclic acetals.

EXPERIMENTAL SECTION

The gaseous acylium ion $(CH_3)_2NCO^+$ was produced from self-dissociation of the highly labile protonated TMU under both ESI and APCI conditions. The ion reacts with the neutral acetal in the API source, and the products of the reaction were analyzed with either single- (MS) or double-stage (MS^2) mass spectrometric experiments performed with a tandem QTof (Manchester, U.K.) hybrid (quadrupole (Q), hexapole collision cell, time-of-flight (TOF)) mass spectrometer. Acetal solutions doped with TMU (1 mg of the acetal and 1 μL of TMU dissolved into 1.5 mL of solvent) were prepared in different solvents: benzene, toluene, water, and 1:1 water/methanol solutions. Care should be taken, however, to select solvents as they must be inert toward reaction with the acylium ion.[13−15] For instance, acetonitrile (a common ESI and APCI solvent) should be avoided because acetonitrile (and other nitriles) reacts efficiently with $(CH_3)_2NCO^+$ by cyclization via double addition to form 1,3,5-oxadiazinium ions.[13i] To form the

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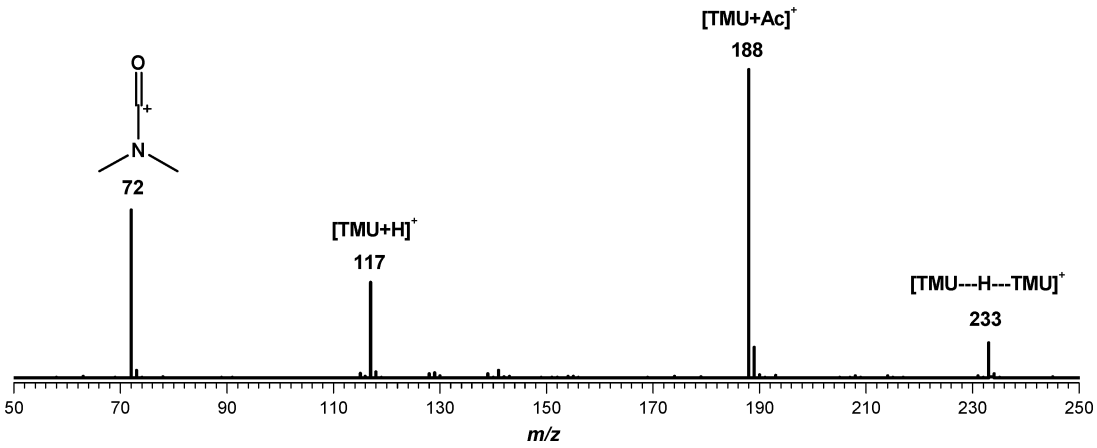


Figure 1. APCI blank mass spectrum for a toluene solution doped with TMU acquired using low cone voltage. Under these low-energy collision conditions, both in-source IMR and in-source dissociation of protonated TMU of *m*/*z* 117 to the $(CH_3)_2NCO^+$ acylium ion (Ac^+) occur. The acylium ion of *m*/*z* 72 reacts further 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. A similar spectrum was obtained under ESI in-source IMR conditions.

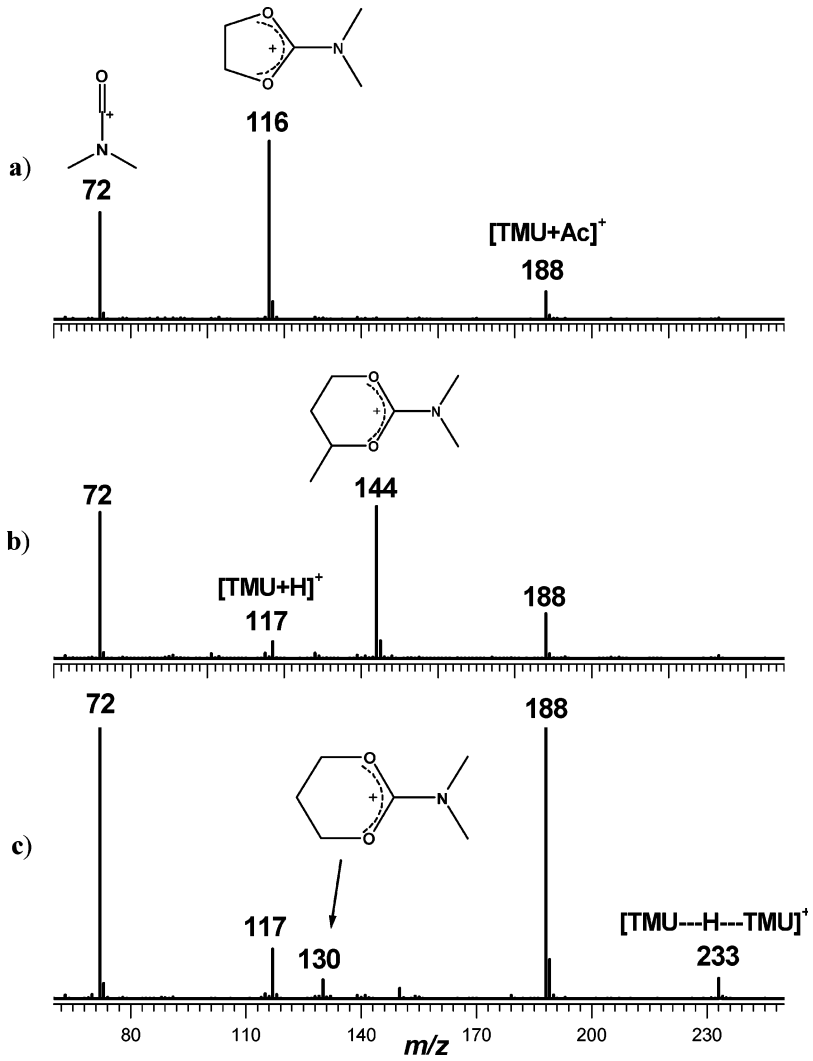
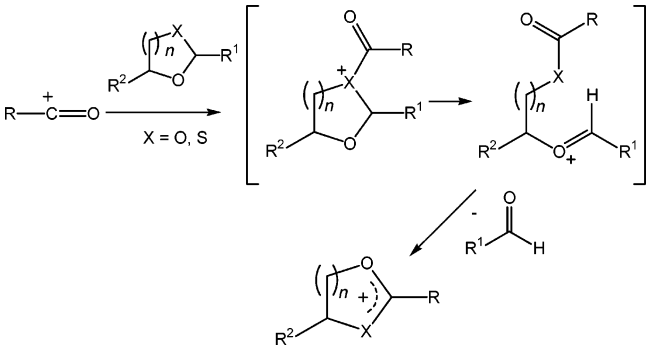


Figure 2. APCI in-source IMR mass spectrum in water/methanol solutions of the acetal (a) **1**, (b) **2**, and (c) **3** with the addition of TMU for in-source generation of the acylium ion $(CH_3)_2NCO^+$ (Ac^+). Note that the TMU background ions were not subtracted.

acylium ion with the highest yield, increase its residential time within the ion source region, and favor its low-energy collisions with the neutral acetal, cone and extractor voltages were set to 1 and 40 V, respectively, whereas capillary (ESI) or needle (APCI) voltages were both set at 4000 V. For the MS^2 experiments, the product ion of interest formed by the in-source IMR was mass-selected by the first quadrupole mass filter for further 15-eV CID with nitrogen in the hexapole collision cell, whereas high-

Scheme 1



resolution mass analysis (5000) for spectrum acquisition was performed by the orthogonal-reflector TOF analyzer.

RESULTS AND DISCUSSION

Proof-of-Principle Reactions. To perform efficient in-source IMR under both APCI and ESI conditions, a neutral dopant needs to function as the precursor of the reactant acylium ion and should meet two crucial criteria: (i) to simplify ion composition in the ionization-plus-reaction region and to maximize the yield of the desired in-source IMR products, the protonated dopant should be sufficiently labile to dissociate easily, and preferentially by a single route, to the desired acylium ion either by metastable decomposition or by the very low, near-zero energy in-source collisions that would be used to *simultaneously* promote both efficient and in-source CID of the protonated dopant and the in-source IMR; (ii) to minimize the undesirable and competitive proton-transfer reaction (which would otherwise promote structurally unspecific protonation of the cyclic acetal), the acylium ion so formed should be both of low acidity and of considerable reactivity toward the desired ionic transacetalization reaction. Fortunately, TMU meets perfectly both of these two criteria: as Figure 1 shows for a TMU solution in benzene (a similar spectrum is obtained for TMU solutions in toluene, water, and 1:1 water/methanol), APCI (as well as ESI) of TMU yields both the protonated molecule of m/z 117 and, most abundantly, the acylium ion $(CH_3)_2NCO^+$ of m/z 72 owing to the high lability of protonated TMU and its ready dissociation by loss of a neutral dimethylamine molecule via metastable decomposition or low-energy in-source CID. $(CH_3)_2NCO^+$ is *the least* acidic and *the most reactive* acylium ion so far tested in gas-phase ionic transacetalization reactions.[14,15] In the ESI environment and under the conditions meant to maximize ion−molecule reactions, a product ion of m/z 188 (the TMU-$(CH_3)_2NCO^+$ adduct) and the TMU proton-bound dimer [TMU- - -H^+- - -TMU] of m/z 233 are both formed to great extent. An appropriate chemical environment for ion−molecule reactions, in which both ready dissociation of protonated TMU to the $(CH_3)_2NCO^+$ acylium ion and efficient low-energy in-source IMR occur, has therefore been established during both ESI and APCI.

Having established an appropriate environment for in-source IMR under both ESI or APCI, we used the same optimized

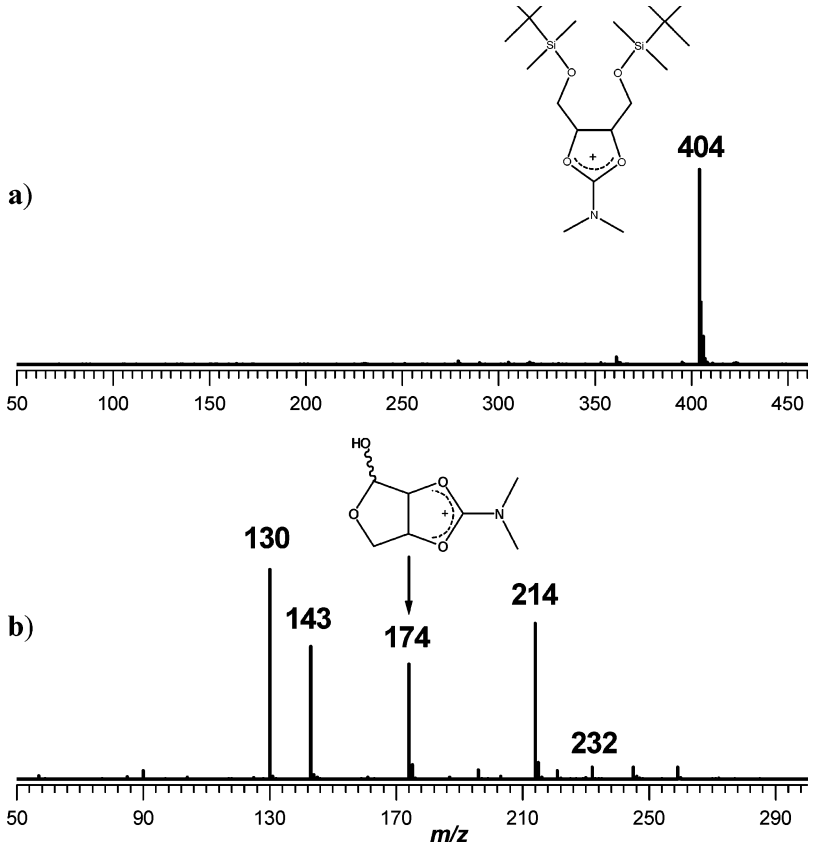
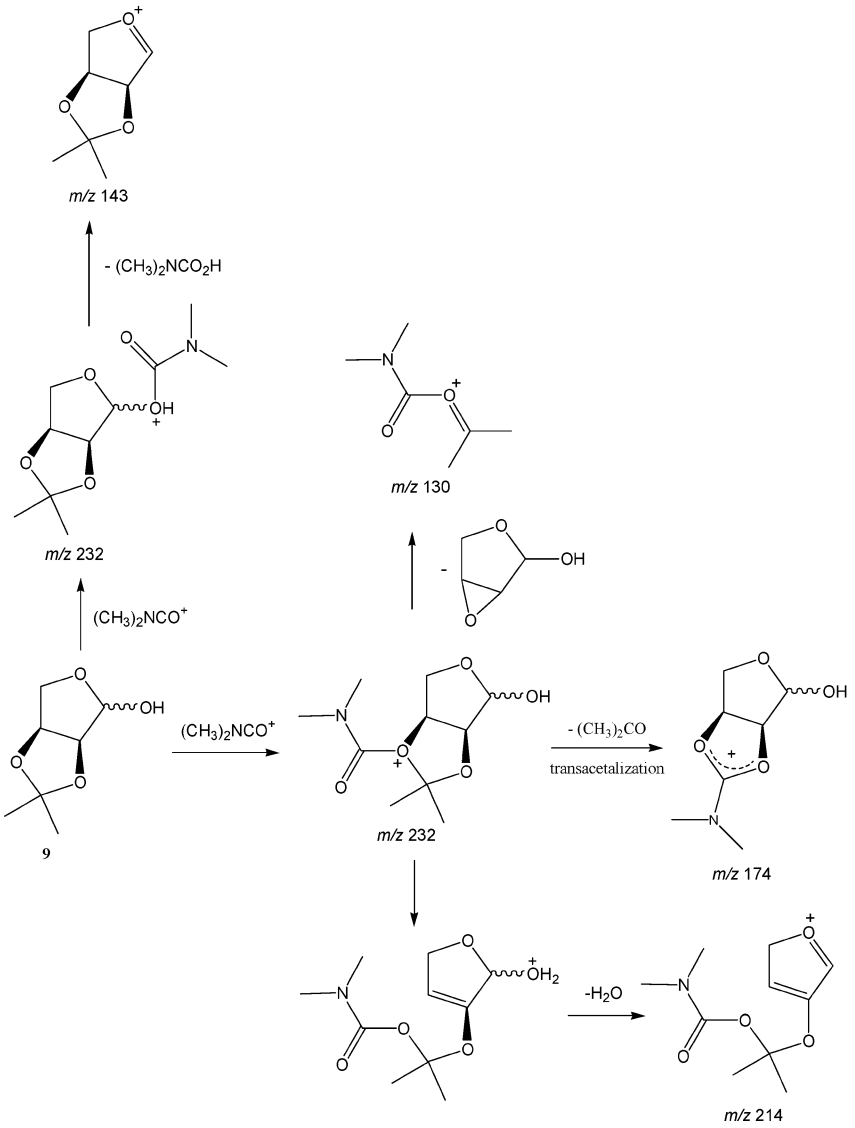
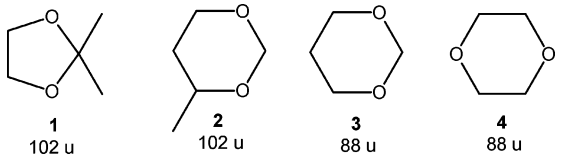


Figure 3. APCI background-subtracted in-source IMR mass spectra from reactions of the acylium ion of m/z 72 with the acetals (a) **6** and (b) **9**. TMU-doped benzene solutions of the acetals were used. Mass spectra for acetals **5**, **7**, and **8** (not shown) also display, as that of (a), the corresponding cyclic ionic acetals as the nearly exclusive product ions owing to favored ionic transacetalization. For product ion assignments in (b), see Scheme 2.

Scheme 2



conditions to perform proof-of-principle reactions with reference cyclic acetals,[15] that is, the structurally simple, low molecular weight, and volatile acetals **1**−**3**. As seen in Figure 2a, by adding



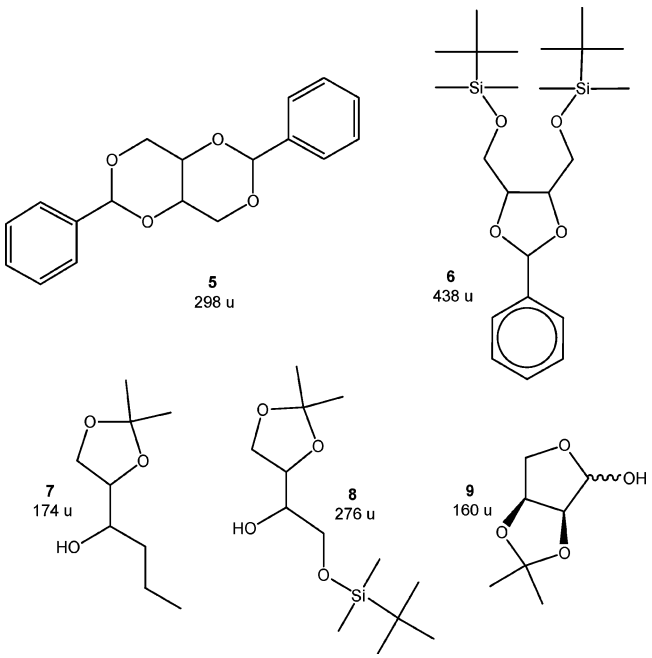
2,2-dimethyl-1,3-dioxolane (**1**) to a TMU-doped toluene solution, an additional (compare to Figure 1), single, and intense product ion of *m*/*z* 116 is formed. This ion is the cyclic ionic acetal formed by ionic transacetalization of the neutral acetal with the acylium ion (Scheme 1).[15a] Note the relatively high, nearly 100% reaction yield as the acetal **1** of 102 u is detected exclusively by its ionic transacetalization product of *m*/*z* 116: acetone (58 u) by acylium ion (*m*/*z* 72) replacement whereas none of the protonated acetal $\mathbf{1}H^+$ of *m*/*z* 105 is formed by the competitive (and herein undesirable) proton-transfer reaction (the highly basic TMU is protonated preferentially). Under mass-selected, more well-defined and controlled tandem mass spectrometry ion−molecule reaction conditions of collision quadrupole cells, protonated acetals (as well as hydride abstraction products) are quite often observed as competitive products.[14,15] Likely under the present ESI and APCI in-source IMR conditions, however, the much more basic neutral TMU competes highly favorably for the proton; hence, protonated acetals are either not formed or do not survive in the high (atmospheric)-pressure TMU-containing gas-phase environment. On the contrary, the competitive acylated TMU product of *m*/*z* 188 is considerably labile reverting upon collisions to the acylium ion, which reacts otherwise irreversibly (owing to the release of the neutral carbonyl product: acetone in Scheme 1) with the acetal by ionic transacetalization, thus forming, for **1,** the major, nearly exclusive cyclic ionic acetal of *m*/*z* 116.[15a]

Figure 2a,b exemplifies a case in which ionic transacetalization functions not only as a class-selective but also as a structurally diagnostic reaction (for acetals in general) with additional isomer distinction. Whereas the acetal **1** is characterized under ESI-(TMU) or APCI(TMU) in-source IMR conditions by its acetone-

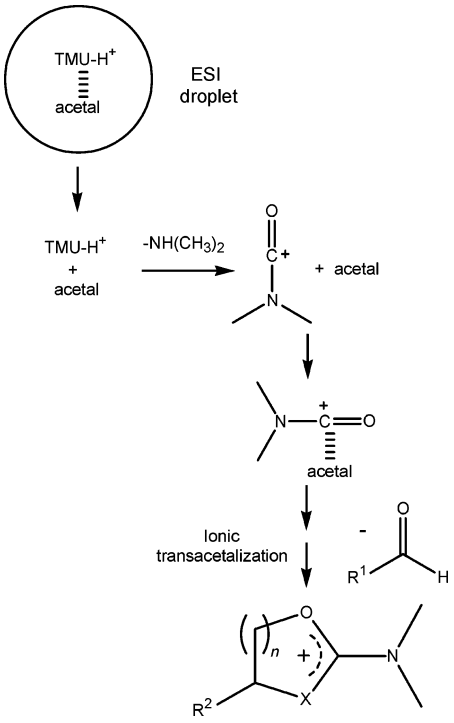
replacement transacetalization product ion of m/z 116 (Figure 2a), the isomeric acetal **2** is characterized by its formaldehyde-displacement ionic transacetalization product ion of m/z 144 (Figure 2b). A direct relationship between the acetal structure and product ion is observed because cyclic acetal substituents at C2 are lost in the course of ionic transacetalization as part of the neutral carbonyl product, whereas ring substituents not placed at C2 remain, thus causing the corresponding mass shift for the cyclic ionic acetal product (Scheme 1). Figure 2c shows another proof-of-principle case in which an 1,3-acetal, 1,3-dioxane (**3**), is distinguished from a nonacetal isomer, its 1,4-dioxo analogue 1,4-dioxane (**4**). Whereas **3** is characterized by its ionic transacetalization product of m/z 130 (Figure 2c) (note that these are non-background-subtracted spectra), its nonacetal isomer **4** (spectrum not shown) yields a mass spectrum with only the TMU characteristic product ions; that is, **4** provides a blank mass spectrum after TMU background subtraction. This is so because **4** is neither basic enough to compete with TMU for the proton, thus none of protonated **4** of m/z 105 is formed, nor a cyclic 1,3-acetal; hence it is also inert toward ionic transacetalization.

TMU Background Subtraction. Because the abundance of the cyclic ionic acetals relative to the ions arising from ESI or APCI in-source IMR of TMU alone (Figure 1) depends on the relative concentrations of the dopant (TMU) and the cyclic acetal, spectrum subtraction is highly desirable as it eliminates the background common product ions arising from TMU reactions (Figure 1). For instance, such a subtraction performed for the spectrum of Figure 2c yields a product ion mass spectrum (not shown) in which the cyclic ionic acetal of m/z 130, the ionic transacetalization product of **3**, fully dominates.

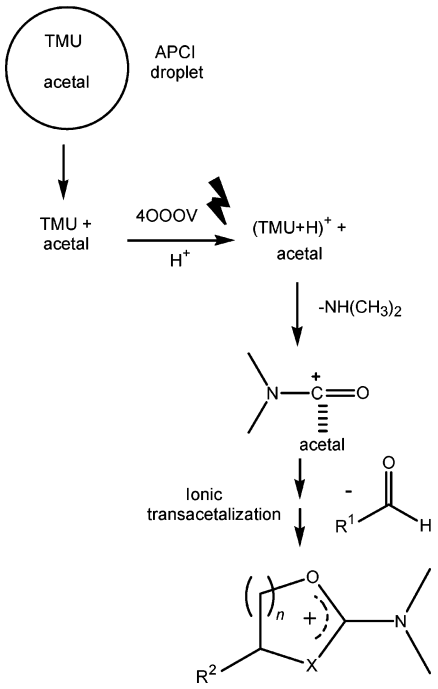
More Structurally Complex, Less Volatile, and Heavier Cyclic Acetals. After we confirmed that ionic transacetalization occurs with the reference cyclic acetals used as proof-of-principle cases, it was important to test the APCI and ESI in-source IMR method for more volatile and heavier cyclic acetals with more complex, multifunctional structures. Five of such acetals **5**−**9** of synthetic importance[16] were selected.



Scheme 3



Scheme 4



As the TMU background-subtracted mass spectrum of acetal **6** of Figure 3a exemplifies, with the formation of the respective and nearly exclusive cyclic ionic acetal of m/z 404, all these acetals react readily by ionic transacetalization upon the APCI or ESI in-source IMR conditions using TMU as the dopant. The TMU background-subtracted spectra of acetals **5**, **7**, and **8** (not shown) also display the respective cyclic ionic acetals as the nearly exclusive product ions. Note the structural diagnostic feature of the mass shift occurring during ionic transacetalization: for instance, acetal **6** of 438 u forms upon reaction with the acylium ion of m/z 72 an ionic acetal of m/z 404 because a neutral molecule

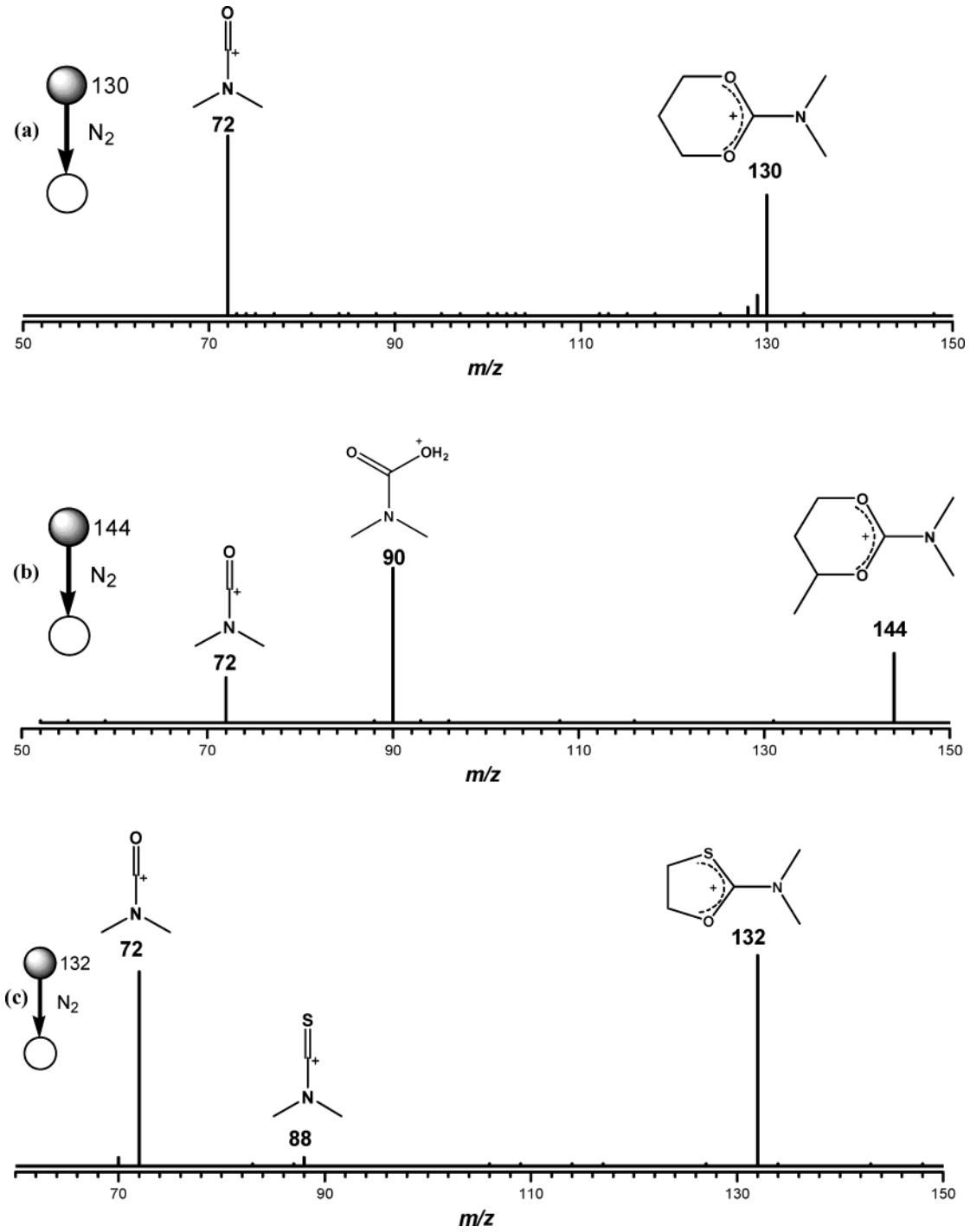


Figure 4. Tandem (MS^2) product ion mass spectra for low-energy CID of the cyclic ionic acetals formed by APCI in-source transacetalization of the acylium ion with (a) 1,3-dioxane, (b) 4-methyl-1,3-dioxane, and (c) 1,3-thioxolane.

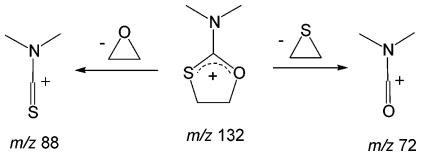
of benzaldehyde of 106 u (438 − 106 + 72 = 404) has been replaced (Scheme 1); hence, we can identify the neutral cyclic acetal as likely bearing at C2 a phenyl group.

Acetal **9** is illustrative since its multifunctional cyclic acetal α-hydroxy ether structure favors not only ionic transacetalization, which forms the cyclic ionic acetal of *m*/*z* 174 (Figure 3b), but also a number of other likewise structurally diagnostic reactions, and major competitive product ions of *m*/*z* 130, 143, and 214 are formed (Scheme 2). Likely, the product ion of *m*/*z* 214 is formed from the nascent adduct by "reaction-induced" water loss owing to an excess of internal energy acquired in the course of reaction; additionally, the product ion of *m*/*z* 143 is formed by hydroxy abstraction whereas that of *m*/*z* 130 also appears to be formed from the nascent adduct of *m*/*z* 232 by a net "acetone abstraction" reaction. Note that hydroxy abstraction is a common, structurally diagnostic reaction of gaseous acylium ions with alcohols, more particularly for α-hydroxy ethers.[17]

Fundamentals of In-Source IMR under APCI and ESI. In-source IMR under ESI or APCI conditions is a novel way to expand

(16) Sabino, A. A.; Pilli, R. A. *Tetrahedron Lett.* **2002**, *43*, 2819.
(17) Moraes, L. A. B.; Eberlin, M. N. *J. Mass Spectrom.* **2002**, *37*, 162.

Scheme 5



the range of molecules toward those of higher mass, polarity, and structural complexity that can be brought to gas phase to react in class-selective and structurally diagnostic fashions. Before, ion−molecule reactions, and in particular ionic transacetalization,[14,15] were limited to more volatile and lighter neutrals as they had to be brought to the gas phase by volatilization or by (ultrafast) heating. Now, with API techniques, considerably more polar and heavier molecules can be transferred to the gas-phase mass spectrometric environment where in-source IMR occur.

(a) ESI. A mechanism for ESI in-source ionic transacetalization can be rationalized using, for instance, the ESI model of ion evaporation (IEM).[3d] Both protonated TMU and the neutral acetal evaporate simultaneously from the ESI droplet solution to the gas phase, then gaseous protonated TMU dissociates readily by dimethylamine loss to form the reactant acylium ion, the acylium ion−acetal complex is formed, and irreversible ionic transacetalization occurs within this gaseous ion−molecule complex yielding the observed product ion, the cyclic ionic acetal (Scheme 3).

(b) APCI. During APCI, both TMU and the cyclic acetal are transferred as neutrals from solution to the gas phase. Likely, corona discharge with ionization by proton-transfer reactions yields mainly protonated TMU, the far more basic neutral. Dissociation of protonated TMU by dimethylamine loss, induced mainly by the excess of internal energy acquired during the exothermic proton-transfer reaction, forms the desirable acylium ion. The gaseous acylium ion−acetal complex is then formed, and ionic transacetalization occurs yielding the observed cyclic ionic acetal product (Scheme 4).

CID Experiments: Product Ion Structural Assignments and Reaction Mechanisms. Most cyclic ionic acetals formed by ionic transacetalization, when mass-selected and subject to low-energy 10−20-eV collisions with argon in the collision cell of the tandem QTOF of mass spectrometer, dissociate to re-form the precursor acylium ion of *m*/*z* 72, as exemplified by that of *m*/*z* 130 from 1,3-dioxane (Figure 4a). Increased structural complexity with the presence of other functional groups or substituents (when placed at positions that favor specific bond cleavages) tend to favor other competitive dissociations, as exemplified for the cyclic ionic acetal of *m*/*z* 144 from **2** (Figure 4b). This ion dissociates competitively to form an abundant fragment ion of *m*/*z* 90 (protonated dimethylcarbamic acid), a process that corresponds to a formal, collision-induced water abstraction reaction.

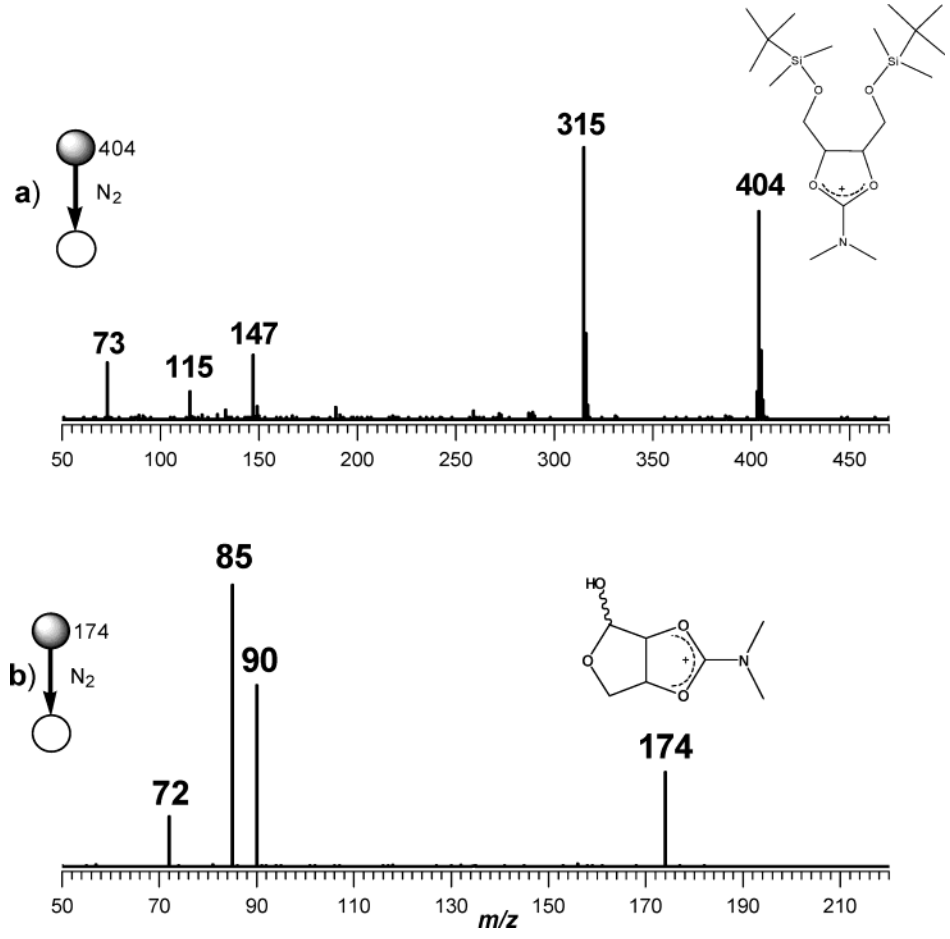


Figure 5. Tandem (MS^2) product ion mass spectrum for low-energy CID of the cyclic ionic acetals formed by transacetalization of the acylium ion with the cyclic acetal (a) **6** of *m*/*z* 404 and (b) **9** of *m*/*z* 174.

Scheme 6

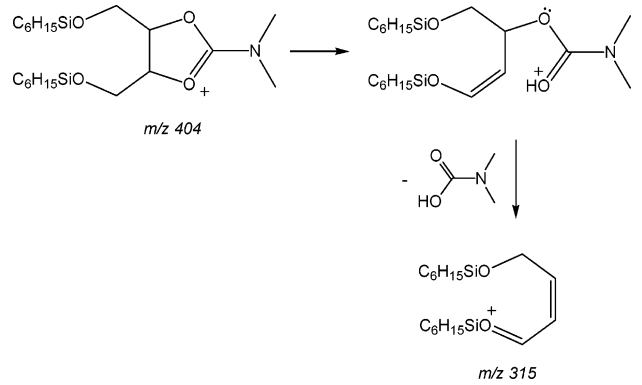


Figure 4c shows the tandem CID product ion mass spectrum of the cyclic ionic acetal formed by ionic transacetalization of the acylium ion with a thioacetal: 1,3-thioxolane (**10**). This reaction

10
90 u

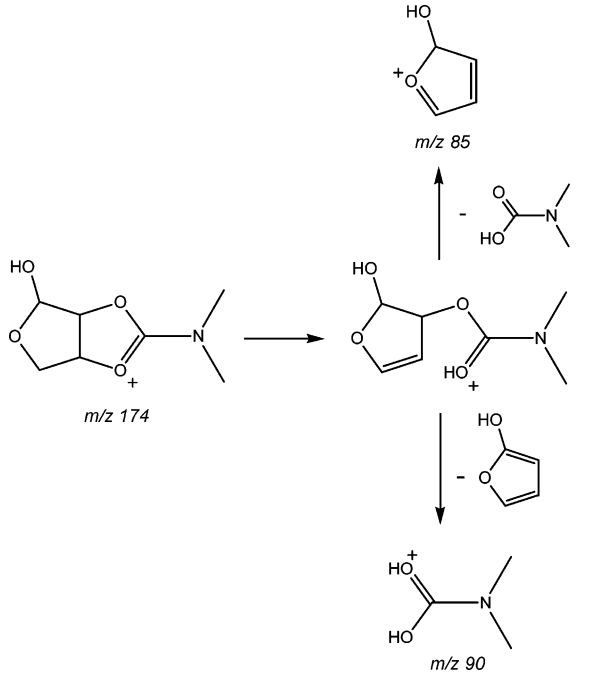
yields both the expected cyclic ionic thioacetal of *m*/*z* 116 and the cyclic ionic thioacetal of *m*/*z* 132, and the CID product ion mass spectrum of *m*/*z* 132 confirms a cyclic structure for the ionic acetals (Scheme 1) since dissociation to both the acylium ion of *m*/*z* 72 and the analogue thioacylium ion of *m*/*z* 88 can only be rationalized with the intermediacy of a cyclic ion (Scheme 5).

The presence of other functional groups with increased structural complexity tends to favor other specific and likewise selective dissociation channels for the cyclic ionic acetals. For instance, the cyclic ionic acetal of *m*/*z* 404 from **6** (Figure 5a) dissociates mainly to the ion of *m*/*z* 315 by *N*,*N*-dimethylcarbamate loss (Scheme 6), whereas that of *m*/*z* 174 from **9** dissociates mainly to the ions of *m*/*z* 90 and 85 (Figure 5b) by the pathways rationalized in Scheme 7 as well as to the more common dissociation to the reactant acylium ion of *m*/*z* 72.

CONCLUSION

Under the unique low kinetic energy in-source ion−molecule reaction conditions used herein for both ESI and APCI, ionic transacetalization of cyclic acetals with the gaseous $(CH_3)_2NCO^+$ acylium ion has been performed with high efficiency. ESI and APCI expand greatly the range of cyclic acetals that can be brought to the gas phase to react by ionic transacetalization. Much heavier, more polar, and less volatile cyclic acetals than those previously employed in reactions performed in quadrupole collision cells have been shown to react efficiently by ionic transacetalization under the ESI and APCI in-source IMR conditions. Tetramethylurea acts as an efficient dopant and can be easily co-injected with the acetal either in benzene, toluene, methanol, or water/methanol solutions. Under the relatively high-pressure, low-energy collision conditions set to favor ESI and APCI in-source

Scheme 7



IMR, $(CH_3)_2NCO^+$ reacts competitively either with TMU to form acylated TMU or with the neutral acetal via the desired ionic transacetalization reaction to form the characteristic class-selective and structurally diagnostic cyclic ionic acetal product ion. Spectra subtraction removes the ionic products of the dopant (TMU) self-reactions, thus providing clean product ion mass spectra. Information on ring substituents can be accessed via characteristic mass shifts resulting from the neutral aldehyde/ketone by acylium ion replacement that occurs upon ionic transacetalization. It has been shown that mixed O/S, O/NH, and S/NH acetals yield two competitive ionic acetal products,[14,15d] which adds to the structural diagnostic capability of the reaction. Enhanced selectivity in structural characterization or chemical recognition for cyclic acetal monitoring is obtained by on-line collision-induced dissociation via tandem mass spectrometric experiments. Most cyclic ionic acetals dissociate exclusively or nearly exclusively to re-form the reactant $(CH_3)_2NCO^+$ acylium ion whereas the presence of additional functional groups with increased structural complexity tends to favor other specific and likewise selective dissociation channels.

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