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Recognition of Cyclic, Acyclic, Exocyclic, and Spiro Acetals via Structurally Diagnostic Ion/Molecule Reactions with the $(CH_3)_2N\text{-}C^+{=}O$ Acylium Ion

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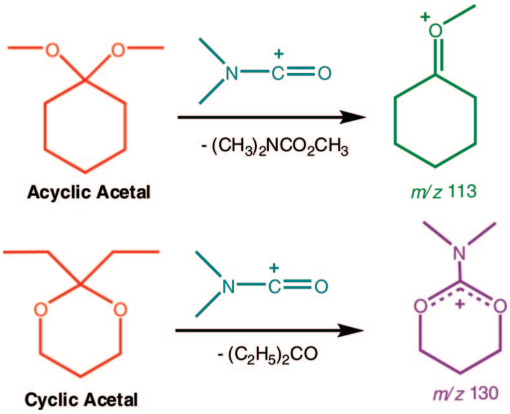

Reactions of the model acylium ion $(CH_3)_2N\text{-}C^+{=}O$ with acyclic, exocyclic, and spiro acetals of the general formula $R^1O\text{-}CR^3R^4\text{-}OR^2$ were systematically evaluated via pentaquadrupole mass spectrometry. Characteristic intrinsic reactivities were observed for each of these classes of acetals. The two most common reactions observed were hydride and alkoxy anion [R^1O^- and R^2O^-] abstraction. Other specific reactions were also observed: (a) a secondary polar [$4^+ + 2$] cycloaddition for acetals bearing α,β-unsaturated R^3 or R^4 substituents and (b) OH^- abstraction for exocyclic and spiro acetals. These structurally diagnostic reactions, in conjunction with others observed previously for cyclic acetals, are shown to reveal the class of the acetal molecule and its ring type and substituents and to permit their recognition and distinction from other classes of isomeric molecules.

Introduction

Reactivity is governed by molecular structure. Chemists have therefore relied heavily on structurally diagnostic reactions to investigate the structure (connectivity and tridimensional arrangement) of molecules of many classes, sizes, and shapes[1] and their reactivities. In solution, however, reactivity is influenced by the environment, that is, mostly by properties of the solvent, solutes, and counter-ions.[2] In the diluted gas-phase environment of mass spectrometers, solvent effects are eliminated[3] and the intrinsic reactivity of isolated molecules and ions can therefore be properly accessed most particularly via tandem

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(1) Shriner, R. L.; Hermann, C. K. F.; Morrill, T. C.; Curtin D. Y.; Fuson, R. C. *The Systematic Identification of Organic Compounds*; John Wiley & Sons: New York, 2003.

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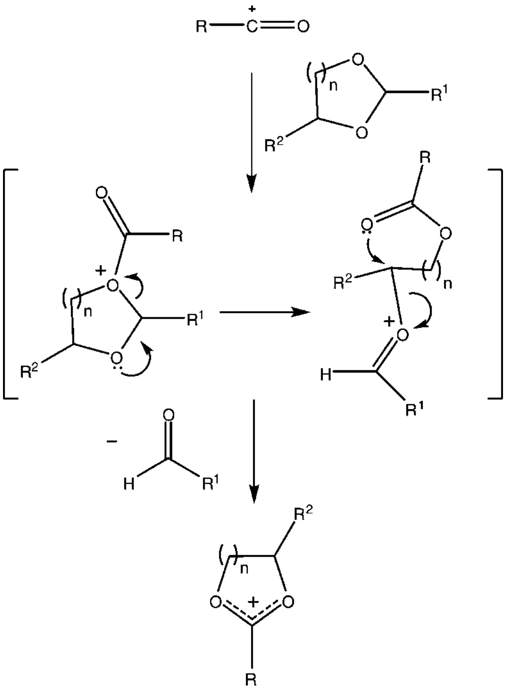
10.1021/jo8008269 CCC: $40.75

SCHEME 1

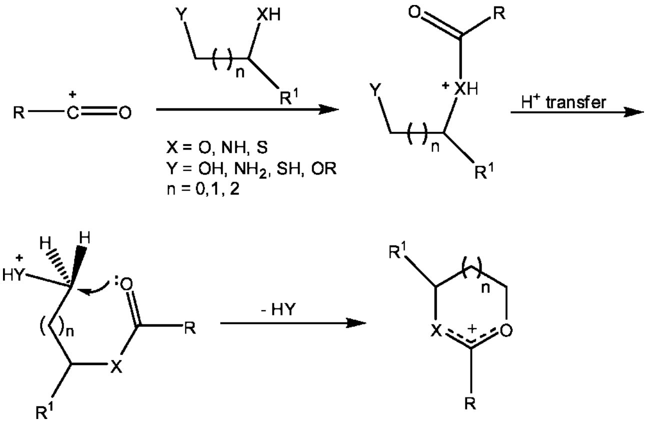


mass spectrometry.[4] Gas-phase ion/molecule reactions have therefore been applied to investigate the intrinsic reactivity as well as the structure of many molecules and ions. Even species that are unavailable or transient in solution have been formed, isolated, and investigated in the gas phase, and many analytical and synthetic applications of these reactions have been described.[5]

A series of structurally diagnostic gas-phase ion/molecule reactions with the ability to provide detailed structural information have been reported.[5] One of these reactions occurs via ionic transacetalization[6] and has become known as the Eberlin reaction.[5i] It employs amphoteric gaseous acylium ions, which possess both Lewis acid and base properties. Studies on the reaction mechanism[7] have shown that this reaction starts with *O*-acylation followed by thermodynamically favored ring opening and recyclization with the release of a carbonyl compound (Scheme 1). A cyclic ionic acetal is formed, and the stability of this resonance stabilized ion has been recognized as the main driving force for the reaction.

The $(CH_3)_2N\text{-}C^+{=}O$ acylium ion is usually employed for it has been found to be the most reactive toward transacetalization as well as toward a similar ionic acetalization reaction[8] with diols and analogues (Scheme 2). Transacetalization and acetalization reactions are highly influenced by structural details and have been shown therefore to work as effective structurally diagnostic gas-phase reactions for cyclic acetals[5i] and diols and their analogues.[8a]

SCHEME 2



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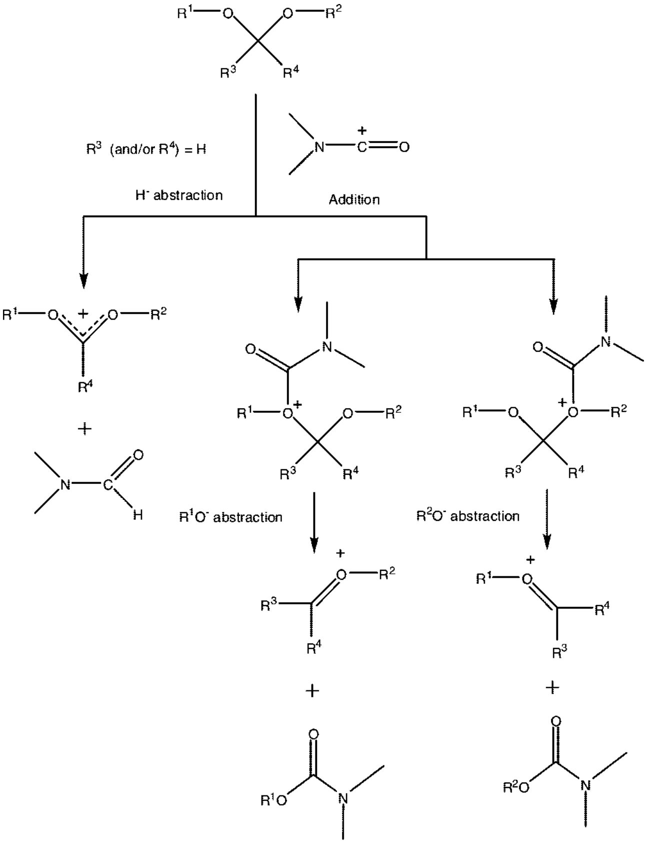

Reactions of acylium ions with acyclic acetals of the $R^1O\text{-}CR^3R^4\text{-}OR^2$ type (Scheme 3) have, however, not yet been reported. Herein, we report a systematic investigation of the intrinsic reactivity of a model acylium ion $(CH_3)_2N\text{-}C^+{=}O$ toward several types of acyclic acetals aimed to determine whether this reaction would serve as structurally diagnostic also for this class of acetals. An overall picture of the applications

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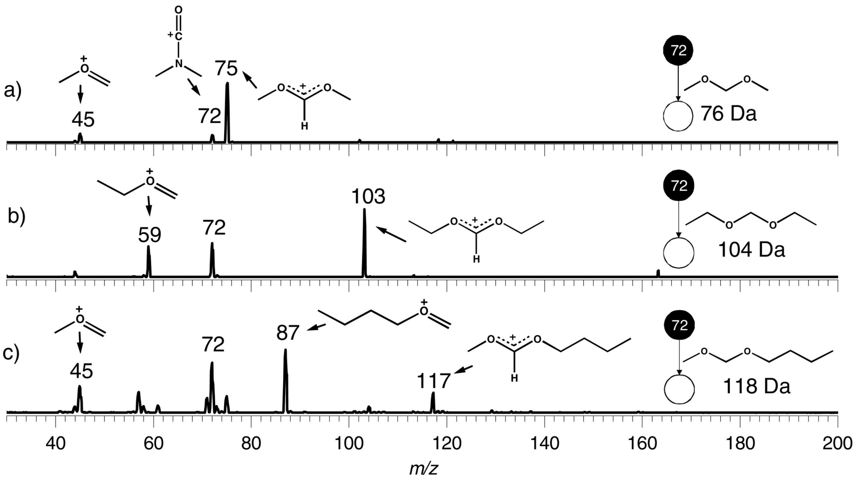

FIGURE 1. Product ion mass spectra for the reaction of $(CH_3)_2N\text{-}C^+{=}O$ of *m/z* 72 with (a) dimethoxymethane, (b) diethoxymethane, and (c) 1-butoxy-1-methoxymethane.[10]

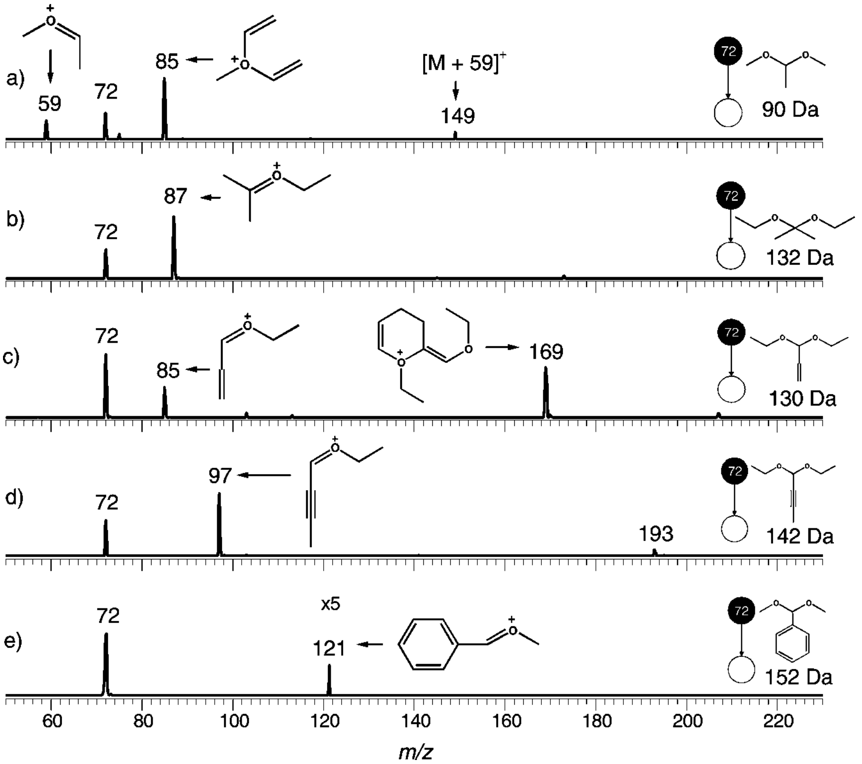

FIGURE 2. Product ion mass spectra for the reactions of $(CH_3)_2N\text{-}C^+{=}O$ of *m/z* 72 with (a) 1,1-dimethoxyethane, (b) 2,2-diethoxypropane, (c) 3,3-diethoxy-1-propene, (d) 1,1-diethoxy-2-butyne, and (e) (dimethoxymethyl)benzene.

of reactions with the gaseous $(CH_3)_2N\text{-}C^+{=}O$ for the recognition and distinction of acetals in general and their isomers is also presented.

Results and Discussions

Reactivity of "Methylene" Acyclic Acetals. Figure 1 shows the reactivity with the gaseous $(CH_3)_2N\text{-}C^+{=}O$ of acyclic acetals of the type $R^1O\text{-}CH_2\text{-}OR^2$, that is, of those containing no substituents on the bridge methylene group ($R^3 = R^4 = H$). For this simple class of acyclic acetals, two reactions were systematically observed: (a) hydride abstraction (H^-)[9] and/or (b) alkoxy anion ($R^{1(2)}O^-$) abstraction (Scheme 3).

For dimethoxymethane (76 Da), H^- abstraction by the acylium ion was found to occur predominantly to yield the product ion of *m/z* 75 (Figure 1a). CH_3O^- abstraction produces the second most abundant product ion of *m/z* 45 (Scheme 3). Likewise, Figure 1b shows that diethoxymethane (104 Da) suffers both H^- and $C_2H_5O^-$ abstraction to form the ions of *m/z* 103 and *m/z* 59, respectively. The reactivity of the

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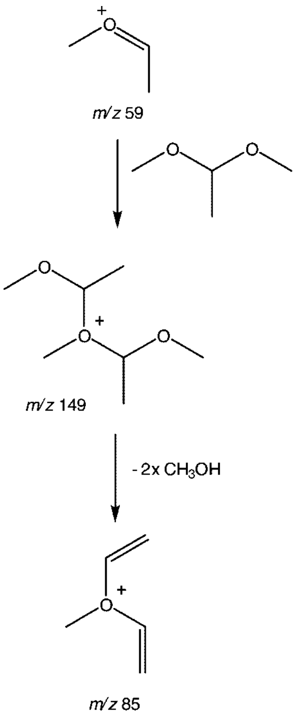
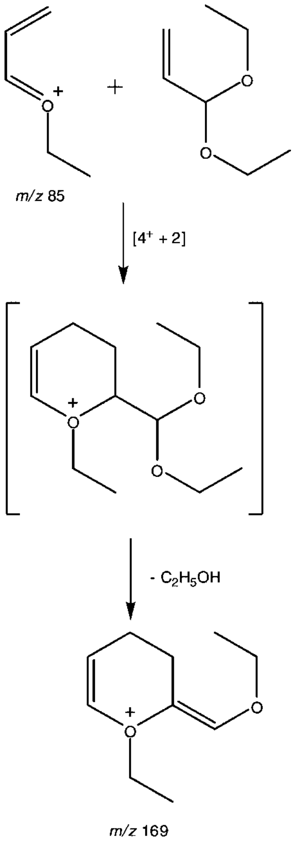
[9] A reviewer has suggested an alternative mechanism for RO^- abstraction involving initial H-abstraction of an α-methylene hydrogen followed by aldehyde loss. For $CH_3OCH_2OCH_3$, for instance, the reaction would involve the following intermediate: $CH_3OCH_2O^+{=}CH_2$ and would form the final product $CH_3O^+{=}CH_2$ by formaldehyde loss. Theoretical calculations at the B3LYP/6-31G(d,p) level showed, however, that the mechanism proposed in Scheme 3 for RO^- abstraction is thermodynamically more favored, by as much as−23 kcal mol^{-1}. A comprehensive theoretical evaluation of this mechanism is underway.

[10] Some unidentified product ions seen in the spectra may arise from secondary reactions, dissociation of reactant or product ions, or impurities of the neutral reactant. Their pathways of formation were not relevant for the present investigation and were therefore not explored in this study.

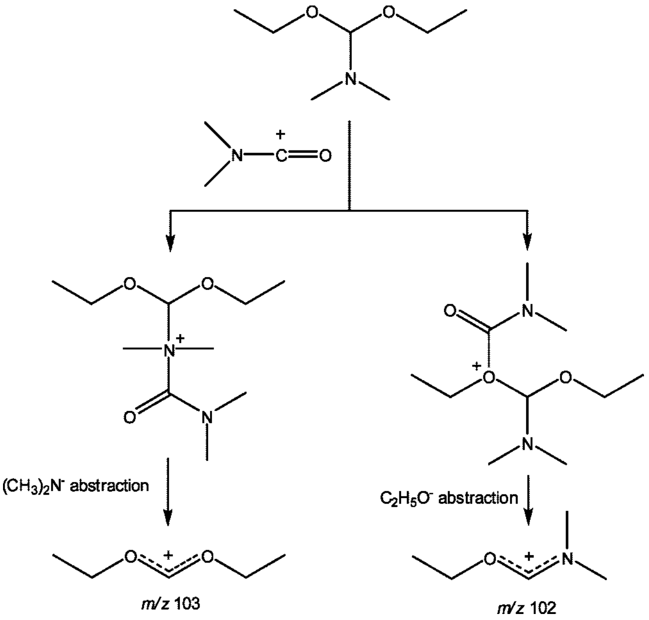
SCHEME 4



SCHEME 5



SCHEME 6



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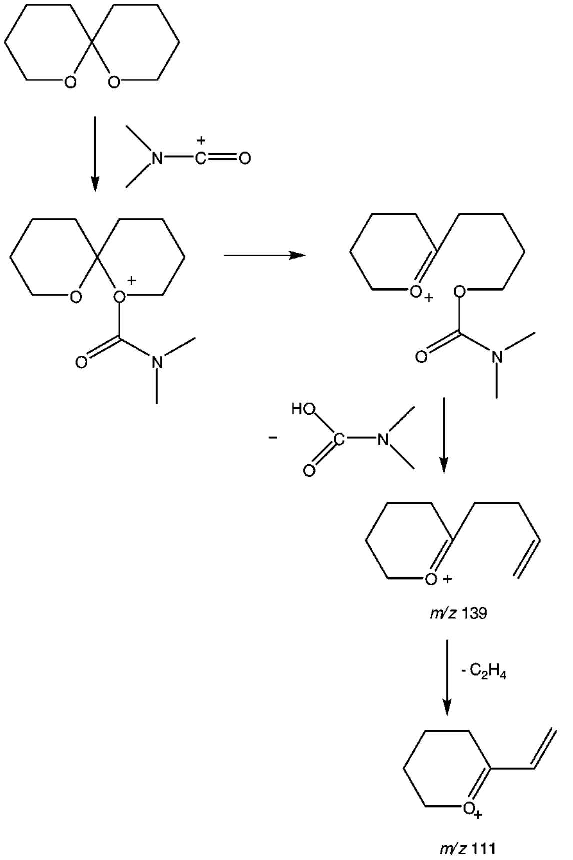

“unsymmetrical” ($R^1 \neq R^2$) acyclic acetal 1-butoxy-1-methoxymethane of 118 Da (Figure 1c) is interesting, from a structural-investigation point of view, since two products from the respective R^1O^- and R^2O^- abstractions could be formed. As expected, H^- abstraction affords the ion of m/z 117 (Scheme 3), whereas both CH_3O^- and $C_4H_9O^-$ abstractions occur concurrently and to great extents yielding the ions of m/z 87 ($CH_2{=}O^+$-C_4H_9) and m/z 45 ($CH_2{=}O^+$-CH_3).

The structurally diagnostic ability of the reaction is therefore evident since the tendencies are (a) methylene-bridged acyclic acetals ($R^1OCH_2OR^2$) to yield both H^- and RO^- abstraction products; (b) symmetrical acyclic acetals ($R^1 = R^2$) to yield a single product from RO^- abstraction (the m/z of this product suggesting the nature of the R group); and (c) unsymmetrical

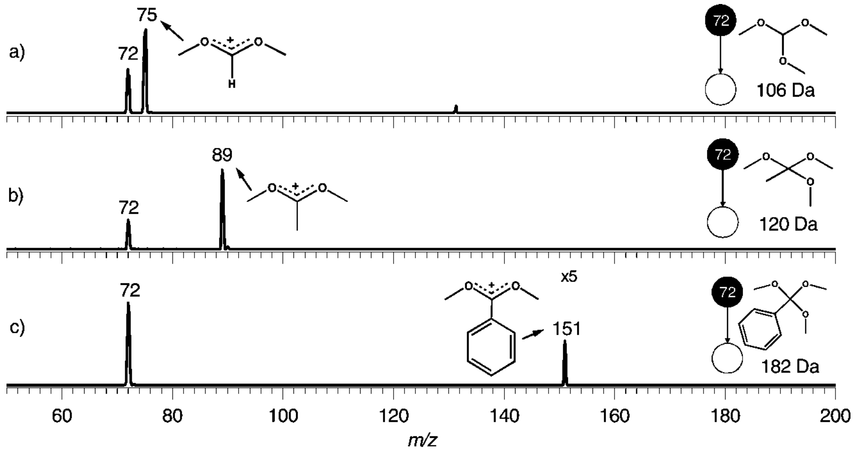

FIGURE 3. Product ion mass spectra for the reactions of $(CH_3)_2N\text{-}C^+{=}O$ of *m/z* 72 with orthoesters: (a) trimethoxymethane, (b) 1,1,1-trimethoxyethane, and (c) (trimethoxymethyl)benzene.

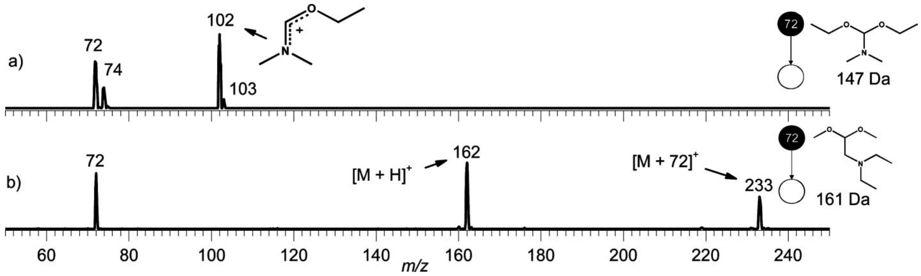

FIGURE 4. Product ion mass spectra for the reactions of $(CH_3)_2N\text{-}C^+{=}O$ of *m/z* 72 with (a) 1,1-diethoxy-*N*,*N*-dimethylmethanamine and (b) 2,2-diethoxy-*N*,*N*-diethylethanamine.

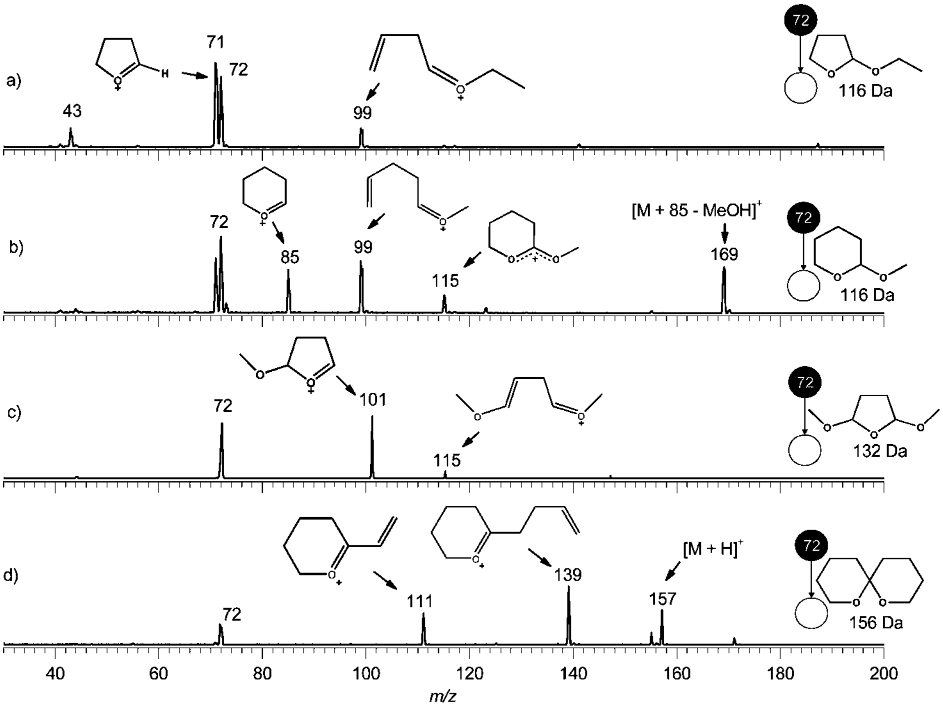

FIGURE 5. Product ion mass spectra (MS^2) for the reactions of $(CH_3)_2N\text{-}C^+{=}O$ of *m/z* 72 with (a) 2-ethoxytetrahydrofuran, (b) 2-methoxytetrahydropyran, (c) 2,5-dimethoxytetrahydrofuran, and (d) 1,7-dioxaspiro[5,5]undecane.

acetals ($R^1 \neq R^2$) to yield two major product ions from R^1O^- and R^2O^- abstractions, as observed for 1-butoxy-1-methoxymethane in Figure 1c.

Reactivity of Alkyl- and Aryl-Substituted Acyclic Acetals. The intrinsic reactivity of acyclic acetals with alkyl and/or aryl substituents (R^3 and/or R^4) at the bridge methylene group

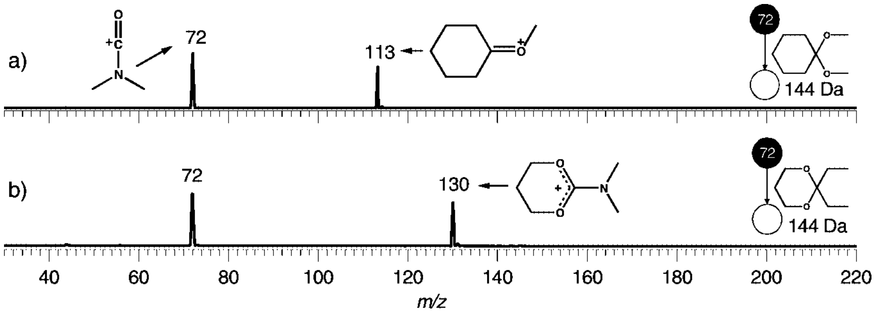

FIGURE 6. Product ion mass spectra for the reaction of $(CH_3)_2N\text{-}C^+{=}O$ of *m*/*z* 72 with (a) 1,1-dimethoxycyclohexane and (b) 2,2-diethyl-1,3-dioxane.

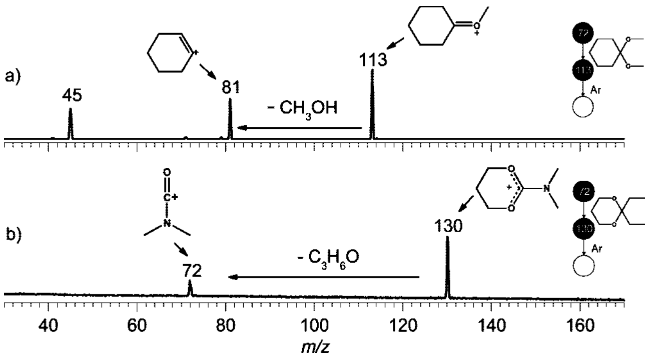

FIGURE 7. Sequential product ion mass spectra (MS^3) for the major product ion formed by the reaction of $(CH_3)_2N\text{-}C^+{=}O$ of *m*/*z* 72 with (a) 1,1-dimethoxycyclohexane (*m*/*z* 113) and (b) 2,2-diethyl-1,3-dioxane (*m*/*z* 130). The structure shown for the ion of *m*/*z* 81 is merely illustrative and is meant to represent the most probable nascent ion that may isomerize to a more stable structure.

was also evaluated (Figure 2). For 1,1-dimethoxyethane ($R^1 = R^2 = CH_3$; $R^3 = H$, $R^4 = CH_3$), H^- abstraction (*m*/*z* 89) is not observed and CH_3O^- abstraction forms a medium abundant product ion of *m*/*z* 59, but the major product ion is that of *m*/*z* 85. Spectra obtained at different pressures of the neutral reactant and also MS^3 structural investigation indicate that this product of *m*/*z* 85 arises from secondary reactions of the CH_3O^- abstraction product of *m*/*z* 59 with the neutral 1,1-dimethoxyethane (M) via the $[M + 59]^+$ adduct of *m*/*z* 149 (Scheme 4). Hence, when this secondary reaction is properly assigned, CH_3O^- abstraction that forms the set of product ions of *m*/*z* 59, 149, and 85 is found to be the predominant primary reaction of 1,1-dimethoxyethane with $(CH_3)_2N\text{-}C^+{=}O$ (Figure 2a).

2,2-Diethoxypropane ($R^1 = R^4 = C_2H_5$; $R^3 = R^4 = CH_3$, 132 Da) again displays no H^- abstraction product (*m*/*z* 131), suffering $C_2H_5O^-$ abstraction to form a single product ion of *m*/*z* 87 (Figure 2b). Three acyclic acetals bearing a single unsaturated alkyl or phenyl substituent at the bridge methylene group, that is, 3,3-diethoxy-1-propene ($R^1 = R^4 = C_2H_5$; $R^3 = H$, $R^4 = CH{=}CH_2$, Figure 2c), 1,1-diethoxy-2-butyne ($R^1 = R^4 = C_2H_5$; $R^3 = H$, $R^4 = C{\equiv}C\text{-}CH_3$, Figure 2d), and (dimethoxymethyl)benzene ($R^1 = R^4 = CH_3$; $R^3 = H$, $R^4 = Ph$, Figure 2e) also react mainly by RO^- abstraction (either $C_2H_5O^-$ or CH_3O^-) to form major product ions of *m*/*z* 85, 97, and 121, respectively. 3,3-Diethoxybut-1-yne is, however, unique since it forms an additional and abundant product ion of *m*/*z* 169 (Figure 2c). The 1,3-diene nature of the oxonium ion of *m*/*z* 85 confers high reactivity to this gaseous ion toward polar $[4^+ + 2]$ cycloaddition,[11] and thus it reacts further and extensively with neutral 3,3-diethoxybut-1-yne (an α-*β* unsaturated dienophile) to form (after ethanol loss from the intact adduct)[12] the most abundant product ion of *m*/*z* 169 (Scheme 5).

Reactivity of Orthoesters. This class of acyclic acetals ($R^3 = OCH_3$) is characterized by their high reactivity (the most reactive among the classes investigated) toward $(CH_3)_2N\text{-}C{=}O^+$ and by the formation of very abundant RO^- abstraction products. The ease of RO^- abstraction from orthoesters by gaseous $(CH_3)_2N\text{-}C^+{=}O$ probably results from the greater stability of the ionic product, that is, the resonance stabilized 1,3-dioxonium ions. Thus, trimethoxymethane of 106 Da (Figure 3a), 1,1,1-trimethoxyethane of 120 Da (Figure 3b), and (trimethoxymethyl)benzene of 182 Da (Figure 3c) form practically a single and abundant product ion (those of *m*/*z* 75, 89, and 151, respectively) due to CH_3O^- abstraction.

Reactivity of Amino-Substituted Acyclic Acetals. 1,1-Di ethoxy-*N,N*-dimethylmethanamine (Figure 4a) offers an interesting case for reactivity evaluation since either $C_2H_5O^-$ or $(CH_3)_2N^-$ abstraction could occur or both (Scheme 6). The spectrum shows that $C_2H_5O^-$ abstraction largely predominates (the ion of *m*/*z* 103 from $(CH_3)_2N^-$ abstraction is detected as a very minor product). As shown by an MS^3 experiment, the ion of *m*/*z* 74 is a fragment of the $C_2H_5O^-$ abstraction product of *m*/*z* 102 due to ethane loss (28 Da).

2,2-Diethoxy-*N,N*-diethylethanamine offers another interesting case for structural investigation. For this acyclic acetal, only CH_3O^- abstraction is expected since the amino group is not directly connected (*β* position) to the bridge methylene group, but the product ion mass spectrum (Figure 4b) reveals a unique reactivity. This acetal forms two major products: $[M + H]^+$ of *m*/*z* 162 arising from proton transfer and the intact adduct of *m*/*z* 233. We rationalize the formation of the intact adduct for this *β*-amino acetal via initial addition preferentially at the amino group, which hampers $C_2H_5O^-$ abstraction (Scheme 3).

Reactivity of Exocyclic and Spiro Acetals. The reactivity of some exocyclic acetals and a spiro acetal was also investigated (Figure 5). Note that two of these acetals, that is, 2-ethoxytetrahydrofuran (Figure 5a) and 2-methoxytetrahydropyran (Figure 5b), are isomers of $C_6H_{12}O_2$ composition (116 Da). As now expected, the C_2H_5O-substituted 2-ethoxytetrahy-

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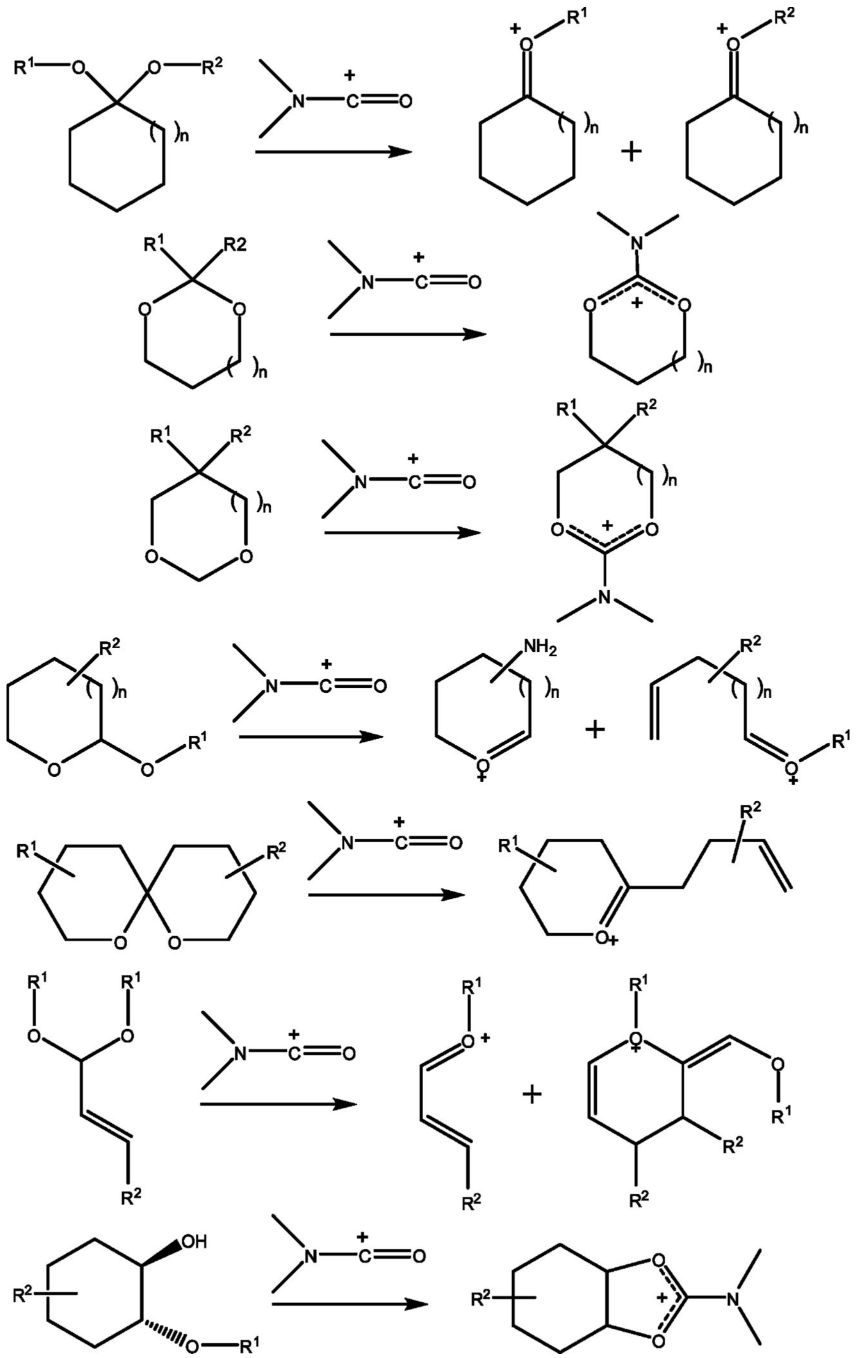
[11] (a) Eberlin, M. N.; Cooks, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 9226–9233. (b) Eberlin, M. N.; Morgon, N. H.; Yang, S. S.; Shay, B. J.; Cooks, R. G. *J. Am. Soc. Mass. Spectrom.* **1995**, *6*, 1–10. (c) Meurer, E. C.; Eberlin, M. *Int. J. Mass Spectrom.* **2001**, *210/211*, 469–482. (d) Meurer, E. C.; Eberlin, M. N. *J. Mass Spectrom.* **2002**, *37*, 146–154. (e) Lemos, A. B.; Sparrapan, R.; Eberlin, M. N. *J. Mass Spectrom.* **2003**, *38*, 305–314. (f) Meurer, E. C.; Sparrapan, R.; Eberlin, M. N. *J. Mass Spectrom.* **2003**, *38*, 1075–1080.

[12] Augusti, R.; Gozzo, F. C.; Moraes, L. A. B.; Sparrapan, R.; Eberlin, M. N. *J. Org. Chem.* **1998**, *63*, 4889–4897.

SCHEME 8

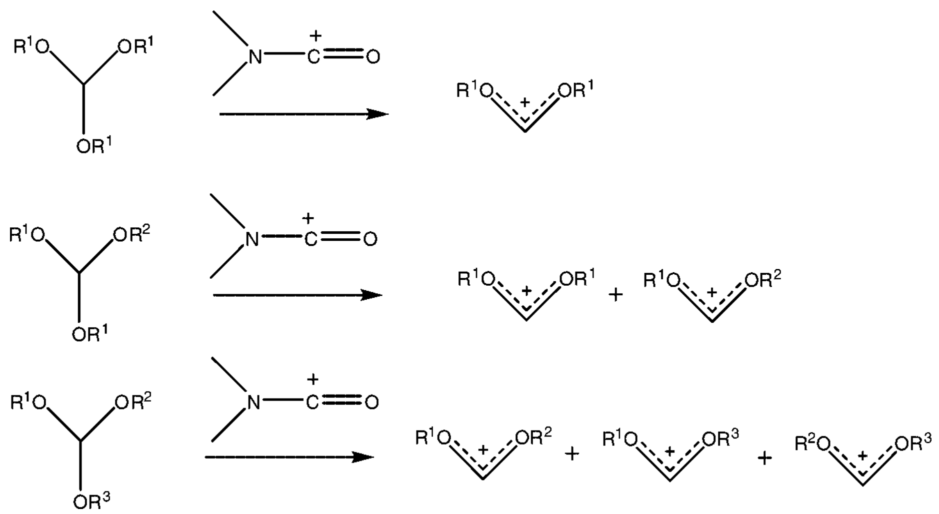


drofuran of 116 Da (Figure 5a) suffers preferentially $C_2H_5O^-$ abstraction to form the cyclic oxonium ion of *m*/*z* 71. A second product ion of *m*/*z* 99 arising by OH^- abstraction (a novel reaction channel, see Scheme 7) is also formed. The isomeric CH_3O-substituted 2-methoxytetrahydropyran of 116 Da reacts accordingly mainly to form the CH_3O^- abstraction product of *m*/*z* 85, whereas the OH^- abstraction product of *m*/*z* 99 and the H^- abstraction product of *m*/*z* 115 are also observed (Figure 5b). A secondary reaction for the CH_3O^- abstraction product of *m*/*z* 85 is also observed; that is, the ion reacts further with the neutral acetal to form the $[M + 85 - CH_3OH]^+$ product of *m*/*z* 169.

2,5-Dimethoxytetrahydrofuran (Figure 5c) bears two methoxy substituents at the 2- and 5-ring positions, constituting therefore a "doubly exocyclic" acetal. This dimethoxy-substituted acetal reacts with $(CH_3)_2N\text{-}C^+{=}O$ to a great extent to form the corresponding CH_3O^- abstraction product; that is, the cyclic oxonium ion of *m*/*z* 101, whereas OH^- abstraction forms the minor product of *m*/*z* 115 (Figure 5c).

1,7-Dioxaspiro[5,5]undecane offers another interesting case for reactivity investigation. Its spiro structure blocks RO^- abstraction and should drive unique reactivity. Indeed, its product ion mass spectrum (Figure 5d) shows predominance of the product ion of *m*/*z* 139 formed by net OH^- abstraction (Scheme 7). A minor product ion of *m*/*z* 157 due to proton transfer (probably from a primary product ion) is also observed. As shown by MS^3 experiments, the product ion of *m*/*z* 111 is a fragment of the ion of *m*/*z* 139 (formed probably by the loss of ethylene, Scheme 7).

SCHEME 9



Recognition of Cyclic, Acyclic, Exocyclic, and Spiro Acetals and Analogues. Figure 6 illustrates, for a representative pair of isomers, the structurally diagnostic ability of gas-phase reactions with $(CH_3)_2N\text{-}C^{+}{=}O$, which recognizes the class of the acetal (cyclic or acyclic) and the positions of its substituents. Note that 1,1-dimethoxycyclohexane of 144 Da [Figure 6a, $R^1 = R^2 = CH_3O$; R^3, $R^4 = (CH_2)_4$] suffers exclusively CH_3O^- abstraction (Scheme 3) thus yielding a single product of *m/z* 113. This reactivity indicates that the molecule is a symmetrical dimethoxy acyclic acetal with alkyl substituents at the methylene bridge. In great contrast, the isomeric cyclic acetal 2,2-diethyl-1,3-dioxane undergoes ionic transacetalization[5i] (Scheme 1) to form a single and abundant product ion of *m/z* 130 (Figure 6b).

MS^3 Experiments. The structures of reaction products proposed in this work have been substantiated by collision-induced dissociation via MS^3 experiments (see Supporting Information for representative product ions). Figure 7 illustrates such experiments for two major product ions: (a) the CH_3O^- abstraction product of *m/z* 113 (Figure 6a), which is found to dissociate mainly by the loss of methanol to form a fragment ion of *m/z* 81 and (b) the transacetalization product of *m/z* 130 (Figure 6b), which dissociates by C_3H_6O loss thus releasing the “protected” acylium ion of *m/z* 72. This dissociation is comparable to the hydrolysis of acetals in solution that reforms the carbonyl compound.[6]

General Applications. Schemes 8 and 9 summarize, for several classes of acetals and related compounds, the expected major product ion(s) for ion/molecule reactions with $(CH_3)_2N\text{-}C^{+}{=}O$. Predictions are based on the results reported previously[5i] and herein, which are summarized in Table S1 in Supporting Information. For simplicity, the neutral product is omitted. Note the various possible applications for recognition, fine structural investigation an distinction from isomers.

Conclusions

The model acylium ion $(CH_3)_2N\text{-}C{=}O^{+}$ reacts with acyclic acetals in structurally diagnostic fashions, and characteristic reactivities are therefore observed. Acyclic acetals of several types can be therefore recognized and distinguished by applying this reaction, and information can be obtained for the nature and position of their substituents. As Schemes 8 and 9 summarize, the reaction also serves to distinguish acyclic acetals from their cyclic counterparts and analogues. Although this study has used volatile model compounds and gas-phase reactions under the low pressure conditions inside a mass spectrometer, this approach for structural investigation may also be applied to larger, less volatile molecules using atmospheric pressure ionization techniques such as ESI,[16] DESI,[13] and EASI.[14]

Experimental Section

MS^2 and MS^3 experiments were performed on a pentaquadrupole mass spectrometer,[15] denoted as $Q_1q_2Q_3q_4Q_5$, and composed of a sequential arrangement of three mass analyzing quadrupoles (Q_1, Q_3, Q_5) and two *“rf-only”* ion focusing reaction quadrupoles (q_2, q_4). The q_2 and q_4 quadrupoles were used to perform the ion/molecule reactions or collision induced dissociations (CID) under multiple collision conditions. The acylium ion $(CH_3)_2N\text{-}C{=}O^{+}$ of *m/z* 72 was formed by dissociative 70 eV electron ionization (EI) of tetramethylurea (TMU).[16] TMU was inserted in the EI ion source and formed the ion of *m/z* 72, which was selected by Q_1 and transferred to q_2 for ca. 1 eV ion/molecule reactions with the neutral and gaseous acetal. The ion products were then transferred to Q_5 (via Q_3 and q_4) to acquire the product ion mass spectrum. To investigate the structure of the product ions formed in q_2, triple-stage mass spectrometric experiments (MS^3) were performed. The ion product of interest was selected by Q_3 and transferred to q_4 for 15 eV CID with argon. The fragment ions were then transferred to Q_5 for spectra acquisition. With the exception of 1-butoxy-1-methoxymethane and 2,2-diethyl-1,3-dioxane, all other acetals tested were analytical grade purchased from Sigma-Aldrich.

1-Butoxy-1-methoxymethane was synthesized according to Lorette.[17] To a solution of 2,2-dimethoxy-propane (37.2 mL, 0.3 mol) in benzene (60 mL), under argon, were added anhydrous *n*-BuOH (17.5 mL, 0.3 mol) and *p*-toluenesulfonic acid (60 mg, 0.3 mmol). The resulting mixture was heated to 93 °C (oil temperature), when the azeotrope mixture of benzene and methanol was fractioned distilled. The resulting brown residue was cooled, and a solution of NaOMe in MeOH (51 mg in 1 mL) was added

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rapidly, with stirring, the residue becoming orange. The resulting mixture was distilled (122 °C, oil temperature) under reduced pressure, and the desired product (1-butoxy-1-methoxymethane) was isolated.

2,2-Diethyl-1,3-dioxane was synthesized by adding ethylene glycol (8.2 mL, 0.114 mol) and a few crystals of *p*-toluenesulfonic acid to a solution of 3-pentanone (6 mL, 0.0568 mol) in benzene (50 mL), under argon. The resulting mixture was refluxed using a Dean−Stark apparatus. After a reaction time of 24 h, benzene was distilled at atmospheric pressure. The pressure was reduced, and 2,2-diethyl-1,3-dioxane was isolated.

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Supporting Information Available: Additional MS^3 spectra and summary of major product ion(s) for ion/molecule reactions with $(CH_3)_2N\text{-}C^+{=}O$. This material is available free of charge via the Internet at http://pubs.acs.org.

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