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Novel Ketalization Reaction of Acylium Ions with Diols and Analogues in the Gas Phase

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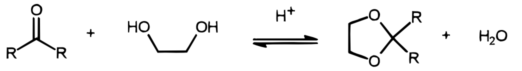
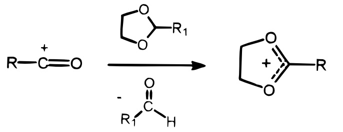
Acetalization or ketalization, which is the conversion of aldehydes and ketones to cyclic acetals and ketals on reactions with diols (eq 1), is a classic, very general, and synthetically useful reaction in the condensed phase.[1] These reactions are widely employed in organic synthesis for protecting either the carbonyl compounds[1] or alternatively the diols[2] against their most common reaction partners. Whereas the cyclic dioxolane derivatives are inert, for instance, upon powerful nucleophiles and reducing agents, they can, however, be hydrolyzed easily to reform both the original diol and the carbonyl compound. Transacetalization[2] with a second aldehyde or ketone also can be used for protection or to reform the reactants.



(1)

In the gas phase, a novel transacetalization reaction of acylium ($RC^+{=}O$), thioacylium ($RC^+{=}S$), and the structurally-related sulfinyl cations ($RS^+{=}O$) was recently reported,[3] in which these "keto" ions displace easily aldehydes and ketones from cyclic acetals or ketals to yield cyclic "ionic ketals", i.e., 1,3-dioxolanylium ions and derivatives (eq 2). The reaction provides a very general method for the gas-phase characterization of the ions[3a,b] and a very selective, gas-phase structurally diagnostic test for a variety of cyclic neutral acetals and ketals, i.e., five-, six-, and seven-membered 1,3-O,O-heterocycles and their sulfur and nitrogen analogues.[3c]



(2)

In the present work, we report that direct *ketalization* of acylium ions also take place to a great extent in gas-phase ion−molecule reactions with a variety of diols and their nitrogen and sulfur analogues and monoalkyl derivatives (Scheme 1). This novel reaction occurs, therefore, in a way that is very similar to condensed phase acetalization or ketalization, and protection of the acylium ions against their most characteristic reactions is attained. Very interesting was also the verification that the acylium ions can be reformed in high yields upon collision-induced dissociation of the cyclic "ionic ketals", a step that is therefore equivalent to the reforming acid hydrolysis of the neutral acetals and ketals in the condensed phase.

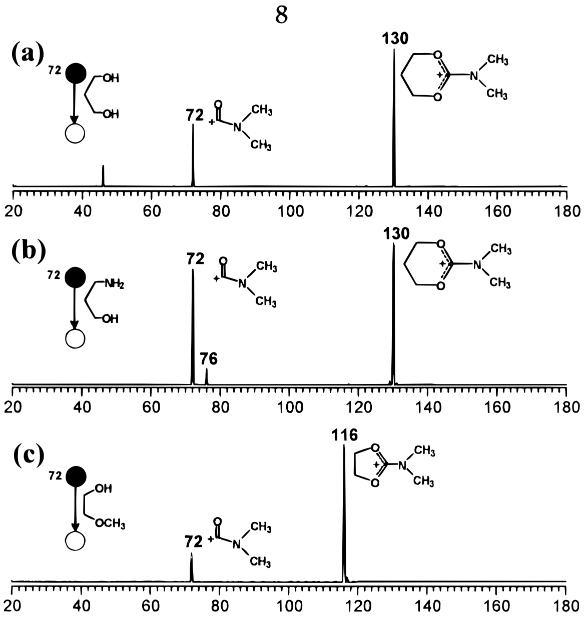


Figure 1. Double-stage (MS^2) product spectra for ion−molecule reactions between the acylium ion $(CH_3)_2NC^+{=}O$ (*m/z* 72) and (a) 1,3-propanediol, (b) 3-amino-1-propanol, and (c) 2-methoxyethanol.

Scheme 1

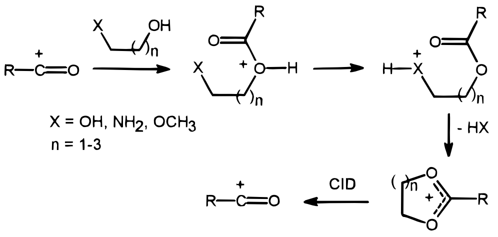


Figure 1a−c shows the double-stage (MS^2) product spectra for reaction between the acylium ion $(CH_3)_2NC^+{=}O$[4] with 1,3-propanediol, 3-amino-1-propanol, and 2-methoxyethanol. The reactions were performed in the reaction chamber of a pentaquadrupole mass spectrometer,[5] a very convenient "laboratory" for gas phase ion−molecule reaction studies.[6,7] Ionic products, which cor-

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(1) Carey, F. A.; Sunderberg, R. J. *Advanced Organic Chemistry*, 2nd ed.; Plenum Press: New York, 1984.

(2) Kunz, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 59, p 659.

(3) (a) Eberlin, M. N.; Cooks, R. G. *Org. Mass Spectrom.* **1993**, *28*, 679. (b) Gozzo, F. C.; Sorrilha, A. E. P. M.; Eberlin, M. N. *J. Chem. Soc., Perkin Trans. 2* **1996**, 587. (c) Moraes, L. A. B., Gozzo, F. C.; Eberlin, M. N.; Vainiotalo, P. Submitted for publication.

(4) The $(CH_3)_2NC^+{=}O$ acylium ion was selected because it is easily and abundantly generated from 70 eV EI of tetramethylurea and shows high ketalization yields.

(5) Juliano, V. F.; Gozzo, F. C.; Eberlin, M. N.; Kascheres, C.; Lago, C. L. *Anal. Chem.* **1996**, *68*, 1328.

(6) The pentaquadrupole mass spectrometer consists basically of an "on-line" setup of three mass-analyzer quadrupoles (Q1, Q3, and Q5) and two reaction chambers (q2 and q4). In a typical experiment, ions are generated in the ion-source, purified (mass-selected) by Q1, and reacted with a neutral gas introduced in q2 under controlled conditions such as collision energy (tipically at near zero eV) and pressure. Each of the product ions can then be subsequently mass-selected by Q3, and structurally analyzed by either collisional dissociation or structurally diagnostic ion-molecule reactions in q4, while Q5 is scanned to record the spectrum. For more details see ref 5.

(7) For representative examples of the applicability of pentaquadrupole triple-stage mass spectra for the study of gas phase ion−molecule reactions see ref 3 and: (a) Kotiaho, T.; Shay, B. J.; Cooks, R. G.; Eberlin, M. N. *J. Am. Chem. Soc.* **1993**, *115*, 1004. (b) Eberlin, M. N.; Cooks, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 9226. (c) Eberlin, M. N.; Kotiaho, T.; Shay, B. J.; Yang, S. S.; Cooks, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 2457. (d) Gozzo, F. C.; Eberlin, M. N. *J. Am. Soc. Mass Spectrom.* **1995**, *6*, 554. (e) Gozzo, F. C.; Eberlin, M. N. *J. Mass Spectrom.* **1995**, *30*, 1553.

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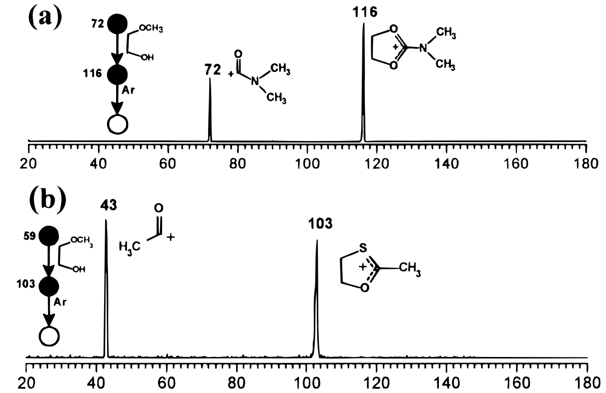
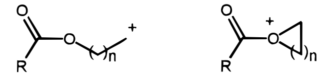


Figure 2. Triple-stage (MS^3) sequential product ion spectra of the product of ketalization (*m*/z 116) of (a) the acylium ion $(CH_3)_2NC^+{=}O$ and (b) the thioacylium ion $CH_3C^+{=}S$ with 2-methoxyethanol.

respond, respectively, to loss of water (*m*/*z* 130), ammonia (*m*/*z* 130), and methanol (*m*/*z* 116) from the unstable adducts, are formed in very high yields, and ketalizations leading to cyclic "ionic ketals" are easily rationalized (Scheme 1). Note that 3-amino-1-propanol and 2-methoxyethanol show interesting regioselectivities. Although in simple amino alcohols and monoalkylated diols the nitrogen atom and the ether group are, respectively, the most likely sites for acylation because of their high nucleophilicity,[1] ketalization proceeds almost exclusively by acylation at the OH group (Scheme 1). Further NH_3 or CH_3OH loss yields the ionic products of *m*/*z* 130 and 116, respectively.

Support for the cyclic "ionic ketal" structures are provided by their pentaquadrupole triple-stage (MS^3) spectra,[7] which show exclusive dissociation to *m*/*z* 72 (Figure 2a) that most likely reforms[8] the reactant acylium ion. Additionally, as expected from the operation of a ketalization mechanism, the spectra of the products of *m*/z 130 formed in reactions with both 1,3-propanediol and 3-amino-1-propanol are nearly identical, whereas the spectra of *m*/*z* 130 and *m*/*z* 116 ions (Figure 2a) are practically the same as those obtained for the authentic cyclic "ionic ketals" formed upon transacetalization of the acylium ion $(CH_3)_2NC^+$dO with dioxane and 2-methyl-1,3-dioxolane, respectively.[3c]

Evidence that appears conclusive about the formation of the cyclic structures is obtained when the putative cyclic "ionic thioketal" formed in high yield upon reactions of $CH_3C^+{=}S$ with 2-methoxyethanol is dissociated (Figure 2b). In this particular case, the $CH_3C^+{=}O$ ion, not the reactant thioacylium ion $CH_3C^+{=}S$, is formed exclusively, a unique dissociation chemistry expected to dominate only if cyclization indeed occurs (Scheme 1). Preliminary results from high level *ab initio* calculations also support formation of the cyclic "ionic ketals", which are shown to be by far the most thermodynamically favorable products, ketalization being considerably exothermic. On the other hand, alternative products such as the ones shown below are found by the calculations to be either unstable or to correspond to unlikely products of endothermic reactions.



It is interesting to note also that the cyclic "ionic ketals" are inert toward a series of reactions that are characteristic for acylium ions. For instance, they form no [4 + 2⁺] cycloadducts[7b] in reactions with isoprene, whereas no transacetalization[3] takes place on reactions with diols or cyclic acetals or ketals, respectively. Therefore, the acylium ions can be considered to be protected in the cyclic "ionic ketal" form, as for the carbonyl compounds in the neutral ketal forms. However, as shown by their triple stage mass spectra, they can be reformed easily upon collision-induced dissociation.

A systematic study of this novel gas-phase reaction, which includes regioselectivity and chain effects for 1,2-, 1,3-, and 1,4-diols and their sulfur and nitrogen analogues and monoalkyl derivatives, is underway in our laboratory. Its applications are also being evaluated. For instance, it is clear that ketalization of acylium ions may be used for their protection or elimination in the gas phase, as well as for their characterization or trapping. Ketalization with acylium ions seems also very promising as structurally diagnostic reactions for a variety of neutral compounds, particularly for a series of biologically relevant molecules for which hydroxy, SH, amino, and ether linkages are among the most common functional groups. Many of these molecules bear these groups in positions that should allow the occurrence of ketalization with acylium ions.

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(8) Structurally diagnostic ion−molecule reactions and pentaquadrupole triple-stage mass spectrometry have shown that the cyclic 2-methyl-1,3-dioxolanylium ion forms almost exclusively (<99%) the acetyl cation upon collision-induced dissociation; see: Eberlin, M. N.; Majumdar, T. K.; Cooks, R. G. *J. Am. Chem. Soc.* **1992**, 114, 2884. Similar behavior is therefore anticipated for other analogous ions.