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Mannich-Type Reactions in the Gas-Phase: The Addition of Enol Silanes to Cyclic *N*-Acyliminium Ions

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The intrinsic gas-phase reactivity of cyclic *N*-acyliminium ions in Mannich-type reactions with the parent enol silane, vinyloxytrimethylsilane, has been investigated by double- and triple-stage pentaquadrupole mass spectrometric experiments. Remarkably distinct reactivities are observed for cyclic *N*-acyliminium ions bearing either endocyclic or exocyclic carbonyl groups. *NH*-Acyliminium ions with endocyclic carbonyl groups locked in *s-trans* forms participate in a novel *tandem* *N*-acyliminium ion reaction: the nascent adduct formed by simple addition is unstable and rearranges by intramolecular trimethylsilyl cation shift to the ring nitrogen, and an acetaldehyde enol molecule is eliminated. An $NSi(CH_3)_3$-acyliminium ion is formed, and this intermediate ion reacts with a second molecule of vinyloxytrimethylsilane by simple addition to form a stable acyclic adduct. *N*-Acyl and *N,N*-diacyliminium ions with endocyclic carbonyl groups, for which the *s-cis* conformation is favored, react distinctively by mono polar $[4^+ + 2]$ cycloaddition yielding stable, ressonance-stabilized cycloadducts. Product ions were isolated via mass-selection and structurally characterized by triple-stage mass spectrometric experiments. B3LYP/6-311G(d,p) calculations corroborate the proposed reaction mechanisms.

Introduction

The Mannich reaction[1] is widely used by both chemists and Nature to form new carbon−carbon bonds via addition of enols or enolates to electrophilic iminium ions. The resulting β-aminocarbonyl compounds (Mannich bases) are versatile synthons that can be converted into a variety of useful derivatives. Important synthetic methodologies known as α-amidoalkylations or Mannich-type condensations also employ the more electrophilic *N*-acyliminium ions,[2] particularly for reactions with less reactive nucleophiles bearing weakly polarized or unpolarized carbon−carbon double bonds. Because of their high reactivity and limited stability, *N*-acyliminium ions are usually generated in situ as transient intermediates by chemical[3] or electrochemical[4] processes. The high diastereo- or stereoselectivity of carbon−carbon bond formation via *N*-acyliminium ion intermediates also allows controlled generation of asymmetric centers.[2]

The gas-phase provides a convenient environment in which to study the intrinsic solvent and counterion free reactivity of ions with neutral molecules,[5] and to screen for potential reactants and model reactions.[6] Multiple-stage mass spectrometry[7] is particularly suitable for such studies, allowing gaseous ions to be formed and isolated via mass-selection and their reactions to be performed under controlled conditions. Many transient ionic inter-

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mediates of solution reactions are often long-lived in the diluted gas-phase environment; hence, they can be mass-selected and their intrinsic gas-phase reactivity conveniently studied. Many *N*-alkyl- and *N*-acyliminium ions can be generated by MS ionization techniques;[8] hence, the bimolecular chemistry of several gaseous iminium and *N*-acyliminium ions has been explored by tanden MS,[9] but no systematic study on their intrinsic electrophilic reactivity has been performed until recently. Using multiple-stage MS, we have compared the intrinsic gas-phase reactivity of several cyclic *N*-alkyl- and *N*-acyliminium ions with endocyclic and exocyclic carbonyl groups toward a model nucleophile: allyltrimethylsilane.[10] An order of cyclic *N*-acyliminium ion intrinsic reactivity was derived and compared with the orders of overall reactivity observed in solution. The corresponding β-silyl cation intermediates were also isolated, for the first time, and their behavior toward dissociation (Grob fragmentation[11]) and ion−molecule reactions investigated. Herein we report on a study of the gas-phase intrinsic reactivity of cyclic *N*-acyliminium ions (including a rare *N*,*N*-diacyliminium ion) in Mannich-type reactions with the parent enol silane: vinyloxytrimethylsilane.

Methods

Double- (MS^2) and triple-stage (MS^3) mass spectrometric experiments[12] were performed with a pentaquadrupole ($Q_1q_2Q_3q_4Q_5$) mass spectrometer[13] and used to mass-select the gaseous iminium ions, to react them with the enol silanes, and to structurally characterize their product ions. The reactant ions were formed from appropriate neutral precursors by 70 eV electron ionization (EI) followed by EI-induced dissociation: **1** (from pyrrolidin-2-one), **2** (from piperidin-2-one), **3** (from *N*-(methoxycarbonyl)pyrrolidine), and **4** (from *N*-acetyl-2-methoxypiperidin-2-one).

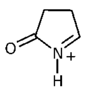
The ion−molecule reactions[14] were performed via MS^2 experiments in which the ion of interest was mass-selected by Q1 and reacted further in q2 at near 1 eV collision energy with the neutral enol silane. To record product ion mass spectra, Q5 was scanned while operating Q3 in the broad band rf-only mode. Multiple collision conditions that caused typical beam attenuations of 50−70% were used in q2 so as to increase reaction yields and promote collisional quenching of both the reactant and product ions.

For the triple-stage (MS^3) experiments, a q2 product ion of interest was mass-selected by Q3 and further dissociated by 15 eV collisions with argon or reacted with pyridine using 1 eV collisions in q4, while scanning Q5 to acquire the sequential product ion mass spectrum. The 15 eV collision energy was taken as the voltage difference between the ion source and the collision quadrupoles. The indicated pressures in each differentially pumped region were typically 2×10^{-6} (ion-source), 8×10^{-6} (q2), and 8×10^{-5} (q4) Torr, respectively.

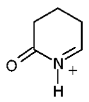
The total energies of optimized geometries for most stable conformations with no symmetry constraints were calculated at the B3LYP/6-311G(d,p) level of theory[15] run on Gaussian98.[16] Details of the optimized structures are available from the authors upon request.

Results and Discussion

Based on our recent investigations of the intrinsic electrophilic reactivity of cyclic *N*-acyliminium[10] and *N*,*N*-diacyliminium ions,[17] four of the most reactive ions were selected: a five- (**1**) and a six-membered ring (**2**) *NH*-acyliminium ion with endocyclic *s-trans* locked acyl groups, a six-membered ring *N*-acyliminium ion with exocyclic *N*-methoxycarbonyl group (**3**), and a six-membered ring *N*,*N*-diacyliminium ion with an exocyclic *N*-acetyl group (**4**). *N*,*N*-Diacyliminium ions are virtually unknown in solution,[2] but their formation, stability and high reactivity in Mannich-type condensation reactions have been recently demonstrated, first in the gas-phase[17] and then in solution.[18]



1



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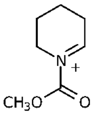

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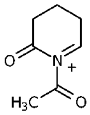

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Cyclic *NH*-Acyliminium Ions with Endocyclic Acyl Groups. MS^2 Experiments. Figure 1 displays the double-stage product ion mass spectra for reactions of **1** and **2** with vinyloxytrimethylsilane (M). Surprisingly, **1** (Figure 1a) forms no stable adduct (*m*/*z* 200), and two unexpected product ions of *m*/*z* 156 and *m*/*z* 272 are

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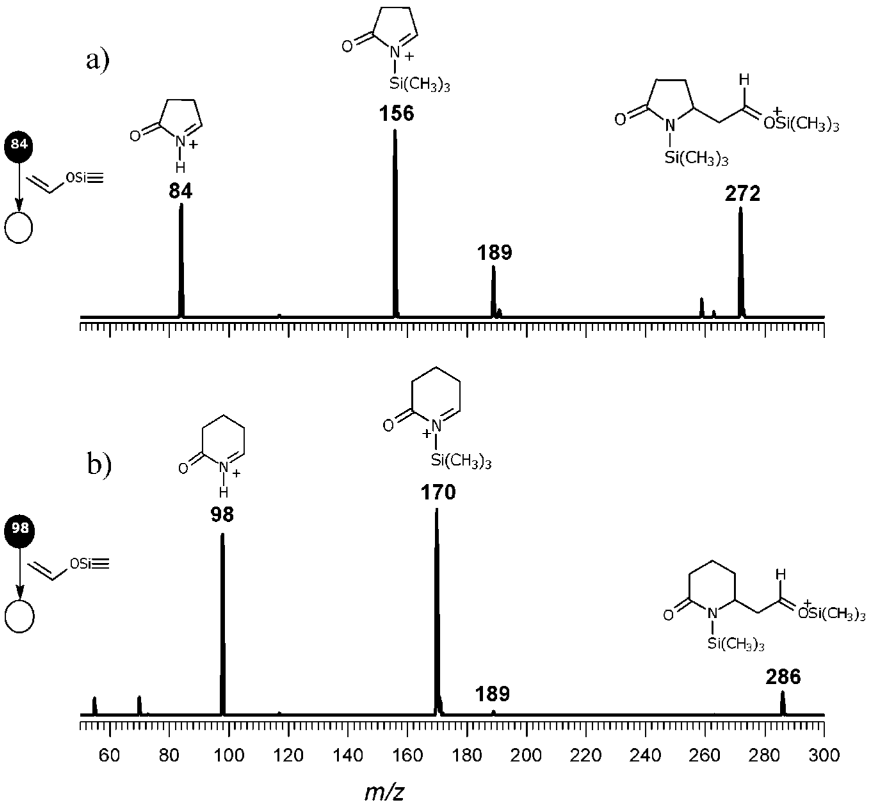


FIGURE 1. Double-stage (MS^2) product ion mass spectra for reactions with vinyloxytrimethylsilane of the cyclic *NH*-acyliminium ions (a) **1** and (b) **2** with endocyclic carbonyl groups.

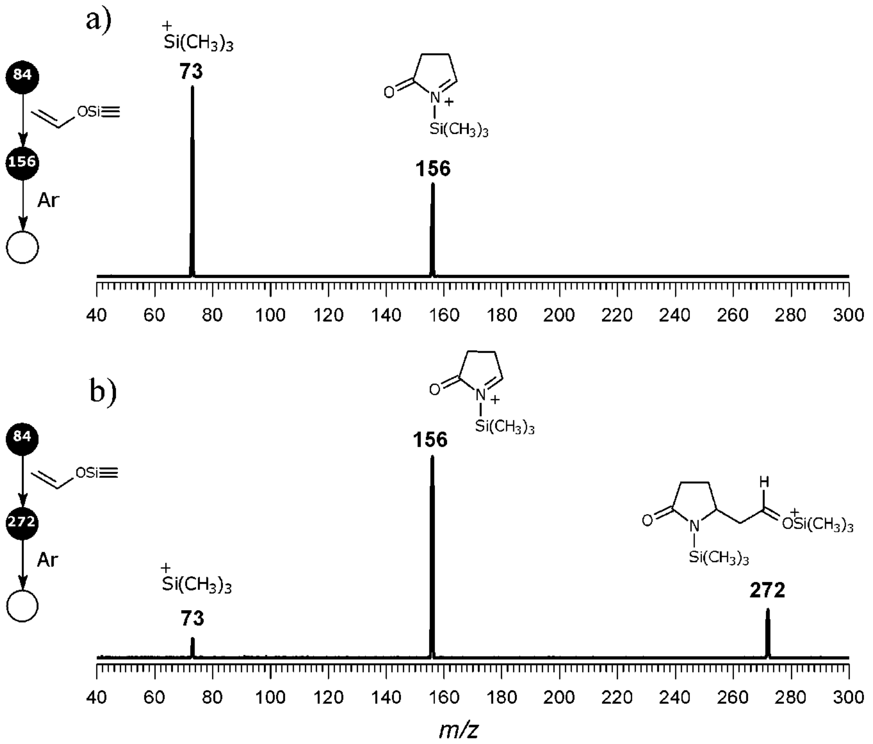


FIGURE 2. Triple-stage (MS^3) CID product ion mass spectra for the product ions of (a) *m*/*z* 156 and (b) *m*/*z* 272 formed in reactions of **1** with vinyloxytrimethylsilane.

formed to great extents.[19] The minor product ion of *m*/*z* 189 is probably formed by $Si(CH_3)_3^+$ transfer to vinyloxytrimethylsilane. Ion **2** behaves similarly to **1** since its reaction with vinyloxytrimethylsilane forms no adduct of *m*/*z* 214 but instead two major product ions of *m*/*z* 170 and 286 (Figure 1b).

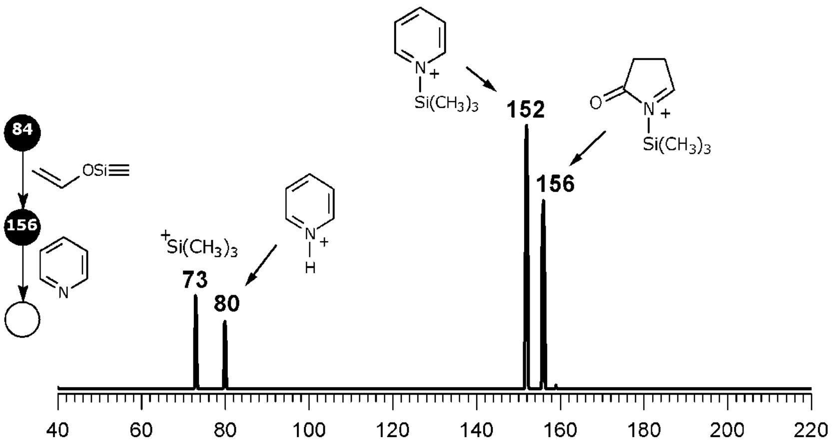


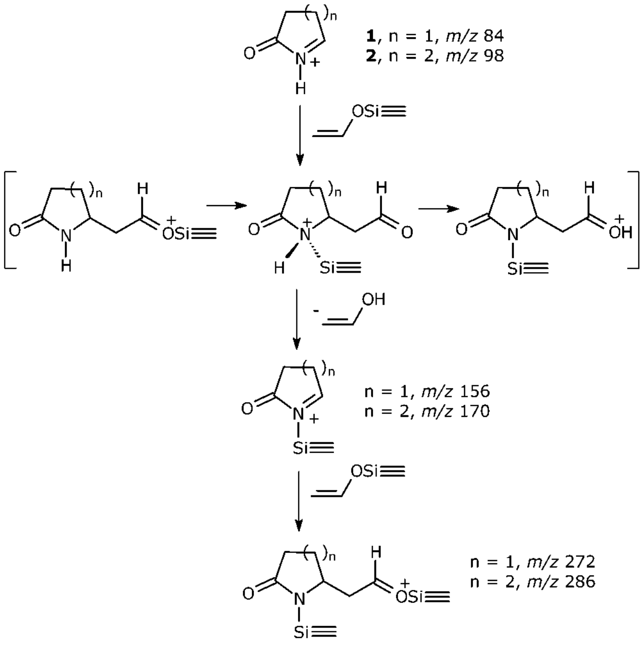
FIGURE 3. Triple-stage (MS^3) product ion mass spectrum for reactions with pyridine of the product ion of *m*/*z* 156 formed in reactions of **1** with vinyloxytrimethylsilane.

MS^3 Experiments. To investigate the structures of the unexpected product ions, triple-stage CID sequential product ion mass spectra were collected for *m*/*z* 272 and 156 from **1** (Figure 2) and for *m*/*z* 286 and 170 from **2** (spectra not shown). Those of *m*/*z* 272 (Figure 2b) and *m*/*z* 286 dissociate exclusively by the loss of a neutral molecule of 116 u (vinyloxytrimethylsilane) to form *m*/*z* 156 and 170, respectively. The product ions of *m*/*z* 156 (Figure 2a) and 170 dissociate exclusively to the trimethylsilyl cation of *m*/*z* 73.

Figure 3 shows the triple-stage sequential product ion mass spectrum for reactions of *m*/*z* 156 with pyridine. Three major product ions are formed: *m*/*z* 152, 80, and 73. The product ion of *m*/*z* 80 is probably protonated pyridine formed either by primary proton transfer from *m*/*z* 156 or from secondary proton transfer from product ions, or from both pathways. The product ion of *m*/*z* 73 is $Si(CH_3)_3^+$ formed probably by CID of *m*/*z* 156 (see Figure 2a). The most interesting and structurally diagnostic product ion is that of *m*/*z* 152, which is formed by $Si(CH_3)_3^+$ abstraction by pyridine.

It therefore appears clear from the data collected from both the MS^2 and MS^3 experiments that the nascent vinyloxytrimethylsilane adducts of **1** and **2** are intrinsically unstable, and that both dissociate promptly by the loss of a common neutral molecule of 44 u. This molecule likely has the C_2H_4O composition, and it originates probably from the vinyloxytrimethylsilane backbone in a dissociation that must be preceded by a $Si(CH_3)_3^+$ shift.

SCHEME 1



The ions of *m*/*z* 156 and 170 so formed then react readily with vinyloxytrimethylsilane to form *stable* adducts of *m*/*z* 272 and 286. Based on this information, a *tandem N-acyliminium ion reaction* is proposed (Scheme 1).

The nascent primary adducts formed by simple addition are unstable, and a favored intramolecular O-to-N [1,5-$Si(CH_3)_3^+$] shift occurs promptly.[20] A subsequent N-to-O intramolecular proton transfer[21] then enables dissociation with the loss of a neutral acetaldehyde enol molecule (C_2H_4O of 44 u), and the cyclic *$NSi(CH_3)_3$*-acyliminium ions of *m*/*z* 156 and 170 are formed. In line

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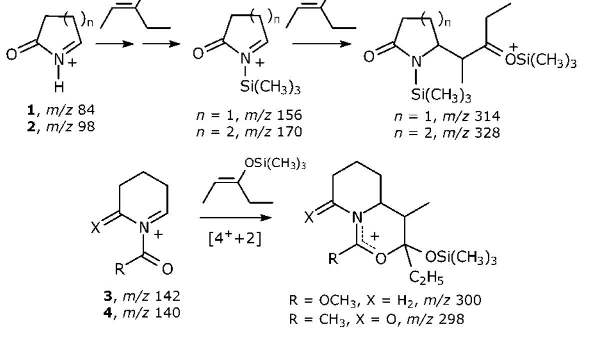
[19] Similar reactivity was observed when the four *N*-acyliminium ions (**1**−**4**) were reacted with another enol silane: 1-ethyl-2-(butenyloxy)trimethylsilane (see Schemes 1 and 4 and the one below).



[20] The large enthalpies of association of $Si(CH_3)_3^+$ with amines (Stone, J. A. *Mass Spectrom. Rev.* **1997**, *16*, 25) suggest that the O-to-N [1,5-$Si(CH_3)_3$] shift is thermodinamically favored, as confirmed by the DFT calculations (see Figure 6).

[21] Attempting to block the N-to-O intramolecular proton transfer, and hence to form a stable adduct, the *NCH_3* analogue of **1** was reacted with vinyloxytrimethylsilane. The ion was found, however, to be inert toward vinyloxytrimethylsilane addition, and the secondary product ion of *m*/*z* 189 (see Figure 1) was formed predominantly. This *NCH_3*-acyliminium ion has also been found to be inert toward allyltrimethylsilane addition.[10]

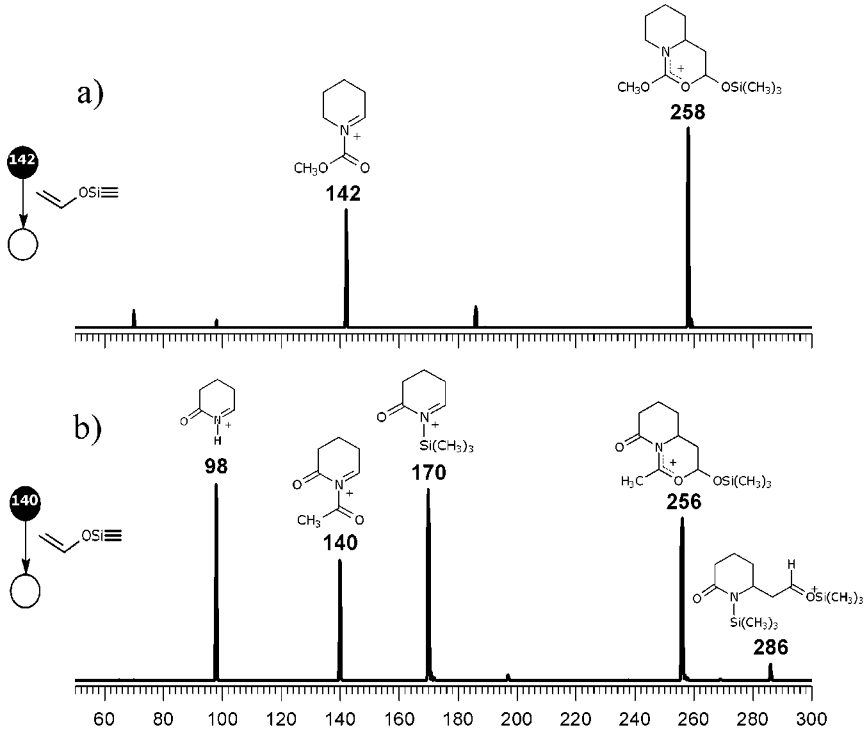
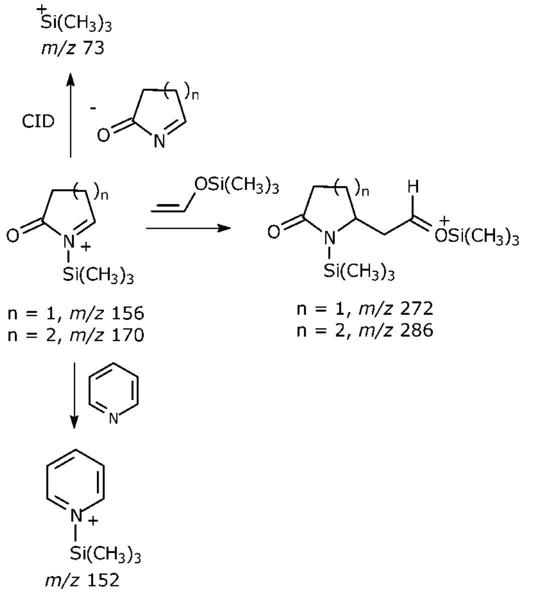


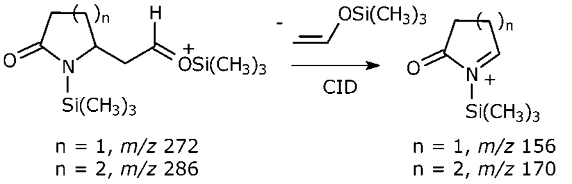
FIGURE 4. Double-stage (MS^2) product ion mass spectra for reactions with vinyloxytrimethylsilane of the cyclic *N*-acyliminium ions (a) **3** and (b) **4** with exocyclic carbonyl groups.

SCHEME 2



with their proposed structures, *m*/*z* 156 and 170 dissociate exclusively to the trimethylsilyl cation of *m*/*z* 73 (Figure 2a). They also react extensively with pyridine by $Si(CH_3)_3^+$ transfer (Figure 3) and with vinyloxytrimethylsilane by simple addition to form the stable adducts of *m*/*z* 272 and 286 (Figure 1, Scheme 2). In analogy with the behavior of the *N*-methyl analogue of **1**, which was found to be inert toward allyltrimethylsilane addition,[10] addition of vinyloxytrimethylsilane to the *NSi(CH$_3$)$_3$*-acyliminium ions of *m*/*z* 156 and 170 occurs not so efficiently as for the corresponding NH-ions of *m*/*z* 84 and 98 (Figure 1), likely because the electron-donating trimethylsilyl group diminishes the ion's electrophilicity.

SCHEME 3



The vinyloxytrimethylsilane adducts of the cyclic *NSi(CH$_3$)$_3$*-acyliminium ions of *m*/*z* 156 and 170, those of *m*/*z* 272 (Figure 2a) and 286, dissociate as expected: retroaddition to *m*/*z* 156 or *m*/*z* 170 dominates (Scheme 3).

***N*-Acyliminium Ions with Exocyclic *N*-Carbonyl Groups. MS^2 Experiments.** Reactions of the *N*-acyliminium ion **3**[19] of *m*/*z* 142 (Figure 4a) and of the *N*,*N*-diacyliminium ion **4** of *m*/*z* 140 (Figure 4b) with vinyloxytrimethylsilane occur mainly by mono addition, and the respective adducts of *m*/*z* 258 and 256 are formed to great extents. The spectrum of Figure 4b shows three additional major ions of *m*/*z* 98, 170, and 286. These product ions are formed because the *N*,*N*-diacyliminium ion **4** of *m*/*z* 140 is quite labile toward dissociation, even upon the very low near 1 eV collision energy applied for the ion–molecule reactions, and a ketene loss[22] that forms **2** of *m*/*z* 98 occurs to a large extent. The *NH*-acyliminium ion **2** then reacts with vinyloxytrimethylsilane as expected (see Figure 2a) to form *m*/*z* 170 and subsequently *m*/*z* 286 (Scheme 1).

MS^3 Experiments. The triple-stage CID sequential product ion mass spectra for the vinyloxytrimethylsilane adduct ions of **3** (Figure 5) and **4** (not shown) were also collected. These adducts dissociate extensively by retro-

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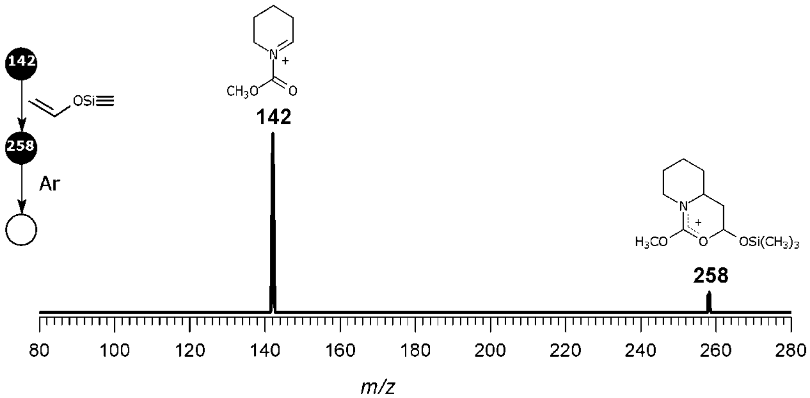

FIGURE 5. Triple-stage (MS^3) CID product ion mass spectrum for the product ion of *m*/*z* 258 formed in reactions of **3** with vinyloxytrimethylsilane.

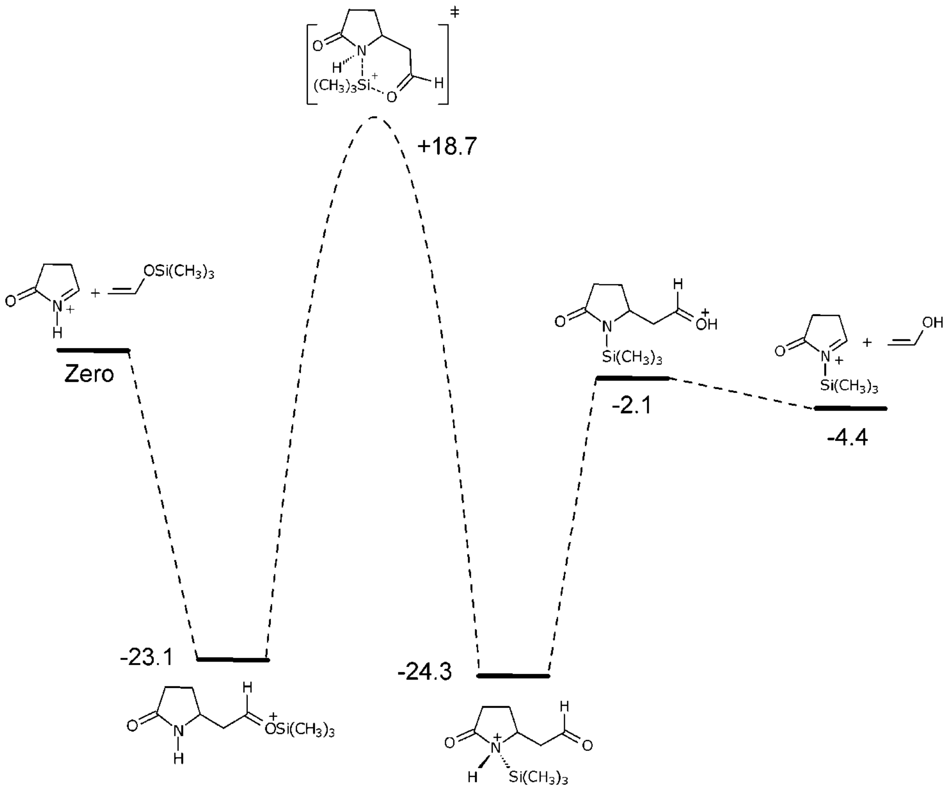

FIGURE 6. B3LYP/6-311G(d,p) potential energy surface diagram for reactions of **1** with vinyloxytrimethylsilane. Energies are given in kcal/mol. Energy barriers were not calculated, expect that for the main [1,5-$(CH_3)_3Si^+$] shift. The energies calculated for the species are, in hartrees: **1** (−285.82429), vinyloxytrimethylsilane (−562.63487), primary adduct (−848.49605), transition state (−848.42937), (secondary adduct (−848.49789), tertiary adduct (−848.46242), N−$Si(CH_3)_3$ substituted *N*-acyliminium ion (−694.60947), acetaldehyde enol (−153.85673). The transition state is characterized by a −163.3 cm^{-1} vibrational frequency.

addition (Grob fragmentation)[11] to yield reactant ions of *m*/*z* 142 and *m*/*z* 140. The dissociation behavior of the vinyloxytrimethylsilane adduct of the *N*,*N*-diacyliminium ion **4** is much richer, however, and has been discussed elsewhere.[17]

Cyclic *N*-acyliminium ions with endocyclic acyl groups are locked in the *s-trans* conformation and are therefore unable to participate as 4-π systems in polar Diels−Alder cycloadditions. But the *s-cis* form required for cycloaddition is considerably more stable than the *s-trans* form[23] for cyclic *N*-acyliminium ions with unlocked exocyclic *N*-alkyl- or *N*-alkoxycarbonyl groups, hence they tend to react by polar [4$^+$ + 2] cycloaddition.[2] In solution, mainly because of the type of π-nucleophiles used, *N*-acyliminium ion cycloadducts participate as transient reaction intermediates and are rarely isolated.[24] Therefore, polar [4$^+$ + 2] cycloadducts[25] have probably been formed in reactions of **3** and **4** with vinyloxytrimethylsilane.[26] For these cycloadducts and contrary to the acyclic adducts of **1** and **2**, no favorable $Si(CH_3)_3{}^+$ shift is available; hence, stable

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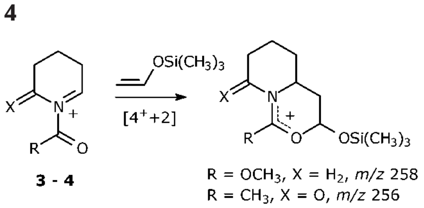
[23] Kupfer, R.; Würthwein, E.-U.; Nagel, M.; Allmann, R. *Chem. Ber.* **1985**, *118*, 643.

[24] A rare example of the isolation of an *N*-acyliminium cycloadduct has been recently reported, see: Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J-. C.; Vanucci, C.; Lhommet, G. *J. Chem. Soc. Perkin Trans 1*, **1997**, 163.

SCHEME 4



cycloadducts are formed (Scheme 4). Upon collision activation, these cycloadducts dissociate extensively by retro cycloaddition, a common and often most favored dissociation of gaseous ionic cycloadducts.[25]

Density Functional Theory (DFT) Calculations. Cyclic *NH*-Acyliminium Ions with Endocyclic Acyl Groups. Figure 6 shows a DFT potential energy surface diagram calculated at the B3LYP/3−311G(d,p) level for the reaction of **1** with vinyloxytrimethylsilane occurring according to the mechanism proposed in Scheme 1. In line with adduct instability observed experimentally, the overall reaction sequence proceeding via adduct dissociation to the cyclic *NSi(CH₃)₃*-acyliminium ion of *m*/*z* 156 is predicted to be overall −4.4 kcal/mol exothermic. Addition of vinyloxytrimethylsilane to **1** is exothermic by −23.1 kcal/mol; then, the intramolecular O-to-N [1,5-Si-$(CH_3)_3{}^+$] shift is also overall exothermic by −24.3 kcal/mol (−1.2 kcal/mol relative to the primary adduct), but the connecting transition state is found to lie 18.7 kcal/mol above the reactants. The extra energy to surpass such a barrier must therefore be provided by kinetic-to-internal energy conversion during collisions. Intramolecular N-to-O proton transfer is endothermic, but the less favored carbonyl-protonated adduct can now dissociate irreversibly by the loss of a neutral acetaldehyde enol molecule, and the *NSi*$(CH_3)_3$-acyliminium ion is formed in an overall −4.4 kcal/mol exothermic process.

Cyclic *N*-Acyliminium Ions with Endocyclic Acyl Groups. Figure 7 shows a potential energy surface diagram for the addition of vinyloxytrimethylsilane to **3**. Both simple addition (−10.2 kcal/mol) and polar [4⁺ + 2] cycloaddition (−35.3 kcal/mol) are predicted to be exothermic, but cycloaddition is more thermodynamically favored by as much as −25.3 kcal/mol. The greater stability of the cycloadduct results, at least in part, from extensive charge delocalization in the dihydro 1,3-oxazinium ion ring.

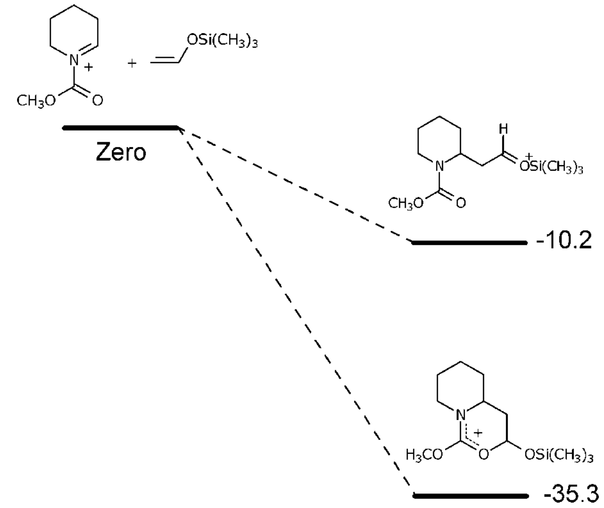


FIGURE 7. B3LYP/6-311G(d,p) potential energy surface diagram for simple addition versus polar [$4^+ + 2$] cycloaddition of **3** with vinyloxytrimethylsilane. Energies are given in kcal/mol. Energy barriers were not calculated. The energies calculated for the species are, in hartrees: **3** (−479.06669), vinyloxytrimethylsilane (−562.63487), simple adduct (−1041.71773), [$4^+ + 2$] cycloadduct (−1041.75786).

Conclusion

The intrinsic reactivity in Mannich-type reactions with the parent enol silane (vinyloxytrimethylsilane) of four of the most reactive cyclic *N*-acyliminium ions has been investigated in the gas phase via multiple-stage mass spectrometric experiments. *N*-Acyliminium ions with endocyclic carbonyl groups locked in *s-trans* forms react via a novel *tandem N-acyliminium ion reaction*: the nascent adducts formed by simple addition are unstable and rearrange by intramolecular O-to-N [1,5-Si$(CH_3)_3$] shift followed by N-to-O proton transfer and then by the elimination of a neutral acetaldehyde enol molecule. *NSi*-$(CH_3)_3$-Acyliminium ions are formed, and these intermediates react (not so efficiently) with a second molecule of vinyloxytrimethylsilane by simple addition to form stable adducts. *N*-Acyl- and *N*,*N*-diacyliminium ions with endocyclic carbonyl groups, for which the *s-cis* conformation is favored, react distinctively by mono polar [$4^+ + 2$] cycloaddition yielding *stable* cycloadducts.

The long-lived gaseous product ions were isolated by mass-selection and structurally characterized by triple-stage mass spectrometric experiments. The structural investigations and B3LYP/6-311G(d,p) calculations corroborate the proposed mechanisms for the gas-phase Mannich-type reactions.

Acknowledgment. This work has been supported by the São Paulo State Research Foundation (FAPESP) and the Brazilian National Research Council (CNPq).

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[25] Polar cycloadditions are common in the gas phase; for recent examples, see: (a) Eberlin, M. N.; Majumdar, T. K.; Cooks, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 2884) (b) Bouchoux, G.; Salpin, J. Y. *Rapid Commun. Mass Spectrom.* **1994**, *8*, 325. (c) Mouregues, P.; Audier, H. E.; Hammerum, S. *Rapid Commun. Mass Spectrom.* **1994**, *8*, 53. (d) Wiegel, K. N.; Holman, R.. W.; Gross, M. L. *Int. J. Mass. Spectrom* **1995**, *146*, 239. (e) Eberlin, M. N.; Sorrilha, A. E. P. M.; Gozzo, F. C.; Pimpim, R. S. *J. Am. Chem. Soc.* **1997**, *119*, 3550. (f) Gevrey, S.; Taphanel, M. H.; Morizur, J. P. *J. Mass. Spectrom.* **1998**, *33*, 399. (g) Chen, Q.; Sioma, C.; Kan, S. Z.; Freiser, B. S. *Int. J. Mass. Spectrom.* **1998**, *180*, 231. 2884. (h) Sparrapan, R.; Mendes, M. A.; Carvalho, M.; Eberlin, M. N. *Chem. Eur. J.* **2000**, *6*, 321.

[26] *N*-vinyliminium ions (*N*-protonated and *N*-methylated 2-aza-1,3-butadiene) have recently been observed to react readily with enol silanes by polar [$4^+ + 2$] cycloaddition, see: (a) Augusti, R.; Gozzo, F. C.; Moraes, L. A. B.; Sparrapan, R.; Eberlin, M. N. *J. Org. Chem.* **1998**, *63*, 4889. (b) Meurer, E. C.; Eberlin, M. N. *Int. J. Mass Spectrom.* **2001**, *210*/*211*, 469.