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Intrinsic Gas-Phase Electrophilic Reactivity of Cyclic *N*-Alkyl- and *N*-Acyliminium Ions

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The intrinsic gas-phase reactivity of cyclic *N*-alkyl- and *N*-acyliminium ions toward addition of allyltrimethylsilane (ATMS) has been compared using MS^2 and MS^3 pentaquadrupole mass spectrometric experiments. An order of electrophilic reactivity has been derived and found to agree with orders of overall reactivity in solution. The prototype five-membered ring *N*-alkyliminium ion **1a** and its *N*-CH_3 analogue **1b**, as well as their six-membered ring analogues **1c** and **1d**, lack *N*-acyl activation and they are, accordingly, inert toward ATMS addition. The five- and six-membered ring *N*-acyliminium ions with *N*-$COCH_3$ exocycclic groups, **3a** and **3b**, respectively, are also not very reactive. The *N*-acyliminium ions **2a** and **2c**, with *s-trans* locked endocyclic *N*-carbonyl groups, are the most reactive followed closely by **3c** and **3d** with exocyclic (and unlocked) *N*-CO_2CH_3 groups. The five-membered ring *N*-acyliminium ions are more reactive than their six-membered ring analogues, that is: **2a** > **2c** and **3c** > **3d**. In contrast with the high reactivity of **2a**, its *N*-CH_3 analogue **2b** is inert toward ATMS addition. For the first time, the transient intermediates of a Mannich-type condensation reaction were isolated—the β-silyl cations formed by ATMS addition to *N*-acyliminium ions—and their intrinsic gas-phase behavior toward dissociation and reaction with a nucleophile investigated. When collisionally activated, the β-silyl cations dissociate preferentially by Grob fragmentation, that is, by retro-addition. With pyridine, they react competitively and to variable extents by proton transfer and by trimethylsilylium ion abstraction—the final and key step postulated for α-amidoalkylation. Becke3LYP/6-311G(d,p) reaction energetics, charge densities on the electrophilic C-2 site, and AM1 LUMO energies have been used to rationalize the order of intrinsic gas-phase electrophilic reactivity of cyclic iminium and *N*-acyliminium ions.

Introduction

Carbocations,[1] owing to their high electron deficiency and inherent reactivity, are widely employed in many methodologies that use their in situ generation and fast and efficient reactions with carbon nucleophiles to form carbon−carbon bonds, a key step in organic synthesis. A foremost example is the Mannich reaction,[2] which is widely used by both chemists and Nature to form carbon−carbon bonds via addition of enols or enolates with strongly polarized carbon−carbon double bonds to simple α-amino carbocations (*N*-alkyliminium ions). For nucleophiles bearing weakly polarized or unpolarized carbon−carbon double bonds, iminium ions activated by *N*-acyl groups (*N*-acyliminium ions)[3] are employed in reactions known as α-amidoalkylations or Mannich type condensations. *N*-Acyliminium ions are generated in situ by chemical[4] or electrochemical[5] processes, and these transient reaction intermediates are broadly applied in important synthetic methodologies.[3] Controlled generation of asymmetric centers is also attained owing to the high diastereo- or stereoselectivity of carbon−carbon bond formation via *N*-acyliminium ions.[3]

In additions of less activated carbon nucleophiles to *N*-acyliminium ions, the electron-attracting *N*-acyl group plays a major role: it enhances reaction rates by increasing the ion's electrophilicity (the electron deficiency on C-2) and makes addition of the carbon nucleophile irreversible and, therefore, synthetically useful.[3]

For reactions with *N*-acyliminium ions, allylsilanes are commonly used as carbon nucleophiles[6] since they display, compared with the analogous olefins, greater nu-

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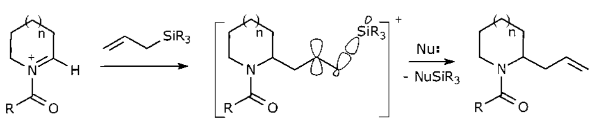
Scheme 1



cleophilicity and regioselectivity. Allylsilanes form β-silyl cation intermediates with enhanced stability provided by the β-silicon effect,[7] that is, the effective overlap between the vacant p orbital on the β-carbon and the σ Si−C orbital (Scheme 1).

The gas phase provides a suitable environment in which to study the intrinsic, solvent, and counterion free reactivity of ions with neutral molecules[8] and to perform fast screening for potential reactants and model reactions.[9] Ionic intermediates, which are transient and highly reactive in solution, are often stable and long-lived in the gas phase, and after mass selection, elaborated studies of their intrinsic reactivity can be performed via tandem mass spectrometric (MS^n) experiments. MS ionization techniques are able to generate many gaseous iminium and *N*-acyliminium ions;[10] hence after mass selection and isolation, their intrinsic reactivity can be investigated and compared. Likewise, if the β-silyl cationic intermediates of α-amidoalkylation are stable and long-lived in the diluted gas-phase environment, they also can be isolated, their participation in α-amidoalkylations as the key reaction intermediates verified, and their intrinsic gas-phase reactivity investigated. The bimolecular chemistry of a few gaseous *N*-alkyl- and *N*-acyliminium ions has been explored by MS techniques,[11] but no systematic study of their intrinsic electrophilic reactivity has been performed.

Herein we report on a systematic study using MS^2 and MS^3 pentaquadrupole mass spectrometric experiments[12] in conjunction with MO calculations of the intrinsic reactivity of gaseous cyclic *N*-alkyl- and *N*-acyliminium ions toward addition of allyltrimethylsilane (ATMS), a nucleophile commonly used in α-amidoalkylations.

Methods

Double- (MS^2) and triple-stage (MS^3) mass spectrometric experiments,[12] performed with an Extrel [Pittsburgh, PA] pentaquadrupole ($Q_1q_2Q_3q_4Q_5$) mass spectrometer,[13] were used to mass-select the gaseous iminium ions, to react them with ATMS, and to structurally characterize their product ions. The reactant ions (see Table 1) were formed from appropriate neutral precursors by 70 eV electron ionization (EI) followed by EI-induced hydrogen atom loss:[10] pyrrolidine (**1a**), *N*-methylpyrrolidine (**1b**), piperidine (**1c**), *N*-methylpiperidine (**1d**), pyrrolidin-2-one (**2a**), *N*-methylpyrrolidin-2-one (**2b**), piperidin-2-one (**2c**), *N*-acetylpyrrolidine (**3a**), *N*-acetylpiperidine (**3b**), *N*-methoxycarbonylpyrrolidine (**3c**), *N*-methoxycarbonylpiperidine (**3d**). For the *N*-methylamines, although the $[M - H]^+$ fragment ions could be conceivably formed by loss of a H atom either from C-2 or from the *N*-methyl group, deuterium labeling experiments with ionized *N*-methylpyrrolidine showed that loss of a C-2 hydrogen dominates as the result of the higher energy necessary to eliminate a primary as compared with a secondary hydrogen atom.[14]

The ion−molecule reactions were performed via MS^2 experiments in which the ion of interest was mass-selected by Q1 and reacted further in q2 with neutral ATMS. Ion translational energies were set to near 1 eV as calibrated by the *m/z* 39:41 ratio in neutral ethylene/ionized ethylene reactions.[15] 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 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 a neutral compound using 1 eV collisions in q4, while scanning Q5 to acquire the product ion mass spectrum. The 15 eV collision energies were 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.

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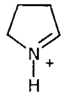
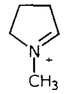
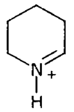
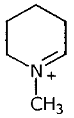
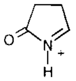
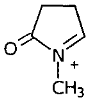
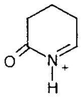
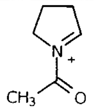
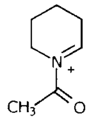
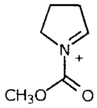
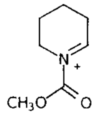
Table 1. Main Ionic Products Formed in Gas-Phase Reactions of the Cyclic *N*-Alkyl- and *N*-Acyliminium Ions 1−3 with ATMS

Reactant ion			**Products**	
		m/z	**β-silyl cation** *m/z* (relative abundance)	**s-ATMS**[a] relative abundance[b]
1a		70	none	100%
1b		84	none	2%[c]
1c		84	none	100%
1d		98	none	2%[c]
2a		84	198 (100%)	8%
2b		98	none	100%
2c		98	87 (100%)	41%
3a		112	240 (3%)	100%
3b		126	240 (6%)	100%
3c		128	242 (100%)	33%
3d		142	256 (50%)	100%

[a] s-ATMS refers to products of secondary ATMS reactions, see text. [b] These relative abundances were calculated by summing the absolute abundances of all s-ATMS products, see text. [c] The reactant ions are of reduced reactivity toward ATMS addition hence most of the selected ions survive collisions and display 100% relative abundance in the product ion mass spectra.

The total energies of optimized geometries for most stable conformations with no symmetry constraints were calculated at the Becke3LYP/6-311G(d,p) level of theory[16] run on Gaussian98.[17] HOMO and LUMO energies were obtained by AM1 semiempirical calculations.[18] Details of the optimized structures are available from the authors upon request.

Experimental Results

Table 1 summarizes the double-stage (MS^2) product ion mass spectra collected for the reactions of the cyclic *N*-alkyl- and *N*-acyliminium ions **1**−**3** with ATMS under conditions (collision energy and pressure) finely adjusted to maximize the yield of the adducts. In these reactions, as indicated by "blank" reactions with a few other ions generated from the same precursors, ATMS ionic fragments and products of further reactions of these fragment ions with neutral ATMS are formed competitively. These reactions are most likely initiated by either hydride or methanide abstraction and form mainly *m/z* 73 [$Si(CH_3)_3^+$], *m/z* 99 [$CH_2{=}CHCH_2Si(CH_3)_2^+$], *m/z* 145 (*m/z* 187 − $CH_2{=}CHCH_3$), *m/z* 187 (ATMS + $Si(CH_3)_3^+$], *m/z*

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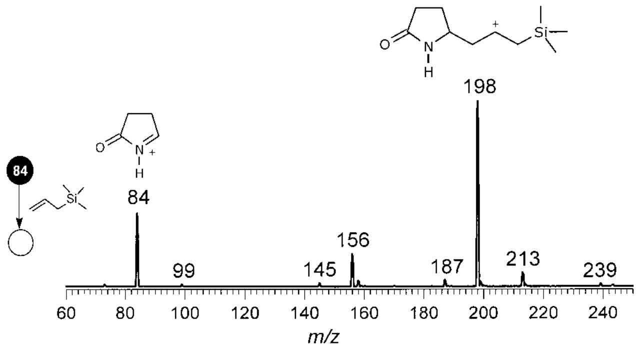


Figure 1. Double-stage (MS^2) product ion mass spectrum for reactions of **2a** with ATMS. Note the abundant β-silyl cation product of m/z 198 and the s-ATMS products of m/z 99, 145, 187, 213, and 239.

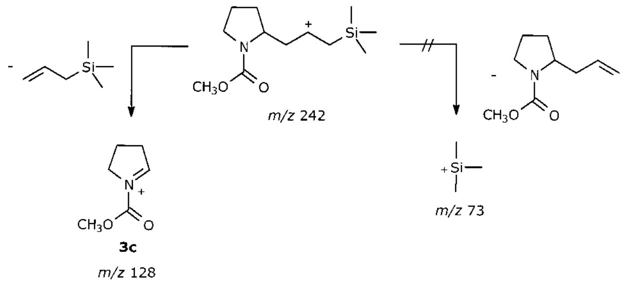
213 [ATMS + $CH_2{=}CHCH_2Si(CH_3)_2{}^+$], and m/z 239, hereafter referred simply as the secondary ATMS (s-ATMS) products. Table 1 lists, for comparison and clarity, the relative abundances of the s-ATMS products as if they were only a single product ion, that is, the s-ATMS relative abundances were calculated by using the sum of the absolute abundances of all the s-ATMS products.

Cyclic *N*-Alkyliminium Ions. The cyclic *N*-alkyliminium ions **1** bearing no *N*-acyl groups fail to form the β-silyl cations expected from ATMS addition. The *N*H-ions **1a** and **1c** form predominantly the s-ATMS products. The *N*-CH_3 ions **1b** and **1d** are virtually inert toward ATMS; they mainly survive the low-energy collisions with ATMS and form only traces of the s-ATMS products.

(a) Cyclic *N*-Acyliminium Ions with Endocyclic *N*-Carbonyl Groups. As Figure 1 exemplifies for **2a**, the *N*-H ions **2a** and **2c** with endocyclic *N*-carbonyl groups react readily with ATMS to form mainly the β-silyl cations. That of m/z 198 for **2a** (Figure 1) and of m/z 212 for **2c** (Table 1) are by far the major products, and the s-ATMS products are minor. If the relative yields of the β-silyl cation and the s-ATMS products (Table 1) are taken as an indication for reactivity toward ATMS addition, **2a** is found to be considerably more reactive than its six-membered ring analogue **2c**. The greater reactivity of **2a** is confirmed in controlled experiments, see below. Remarkably, *N*-CH_3 substitution reduces drastically the reactivity of **2b** as compared with the highly reactive **2a**. With ATMS, **2b** fails to form the β-silyl cation of m/z 212 and the s-ATMS products dominate (Table 1).

(b) Cyclic *N*-Acyliminium Ions with Exocyclic *N*-Acyl Groups. The five- and six-membered ring *N*-acyliminium ions **3a** and **3b** with exocyclic *N*-$COCH_3$ groups are not very reactive toward ATMS addition: they form the expected β-silyl cations of m/z 226 and 240 to limited extents (Table 1). But, in sharp contrast, the analogous *N*-CO_2CH_3 iminium ions **3c** and **3d** react readily. With ATMS, the β-silyl cation of m/z 256 for **3d** and particularly that of m/z 242 for **3c** are formed as major product ions (Table 1).

Scheme 2



The β-Silyl Cations. (a) Formation and Isolation. Figure 2 exemplifies, for **3c**, the series of MS^n (n = 1, 3) pentaquadrupole experiments[12] used to form, isolate via mass-selection, and react the *N*-acyliminim ions and then to select and structurally characterize their gaseous β-silyl cation products. The *N*-acyliminium ion **3c** of m/z 128 is formed abundantly as the $[M - H]^+$ ion by 70 eV EI of *N*-methoxycarbonylpyrrolidine (Figure 2a). After isolation via Q1 mass selection (Figure 2b), **3c** reacts in q2 with ATMS, and a MS^2 product ion mass spectrum is collected (Figure 2c). Nucleophilic ATMS addition occurs readily, and the β-silyl cation of m/z 242 is formed as a major product ion. Then, m/z 242 is isolated by Q3 mass selection (Figure 2d) and structurally characterized both by CID (Figure 2e) and ion−molecule reactions with pyridine (Figure 2f).

(b) Dissociation Behavior. Although two direct and potentially favorable dissociations can be conceived for m/z 242 yielding either the reactant ion or the trimethylsilylium ion (Scheme 2), CID with argon in q4 (Figure 2e) shows that m/z 242 (and the other β-silyl cations) dissociates preferentially and exclusively by retro-addition to re-form the reactant ion **3c** of m/z 128 (which dissociates in turn to m/z 70). This dissociation process, observed here for the first time in the gas phase, is well-known in solution as Grob fragmentation.[19]

(c) Reactivity with Nucleophiles. As Figures 2f and 3 exemplify, the β-silyl cations react with pyridine (selected as a model nucleophile) by two major pathways. That of m/z 242 (Figure 2f) forms m/z 128 likely by unimolecular collision-induced Grob fragmentation,[19] see Figure 2e. Proton transfer, which likely occurs from both the selected reactant ion of m/z 242 and its CID fragment of m/z 128, forms protonated pyridine of m/z 80 (pathway a) that reacts in turn with neutral pyridine to form the pyridine proton-bound dimer of m/z 159 (pathway b, Scheme 3). Finally and most interestingly, the β-silyl cation reacts as anticipated with pyridine to form m/z 152 by $^+Si(CH_3)_3$ abstraction (pathway c).[21]

Similar behaviors are observed for the other β-silyl cations, as further exemplified in Figure 3 for that of m/z

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[17] *Gaussian 98*, Revision A.6. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K. J. B.; Foresman, J.; Cioslowski, J. V.; Ortiz, B.; Stefanov, B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; Gaussian, Inc., Pittsburgh, PA, 1998.

[18] Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

[19] Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.

[20] Note that the gas-phase collision activation that induces dissociation to m/z 128 (Figure 2f) should not occur during nucleophilic attack in solution.

[21] Bimolecular trimethylsilylium ion association and transfer are common in the gas phase, see: Stone, J. A. *Mass Spectrom. Rev.* **1997**, *16*, 25.

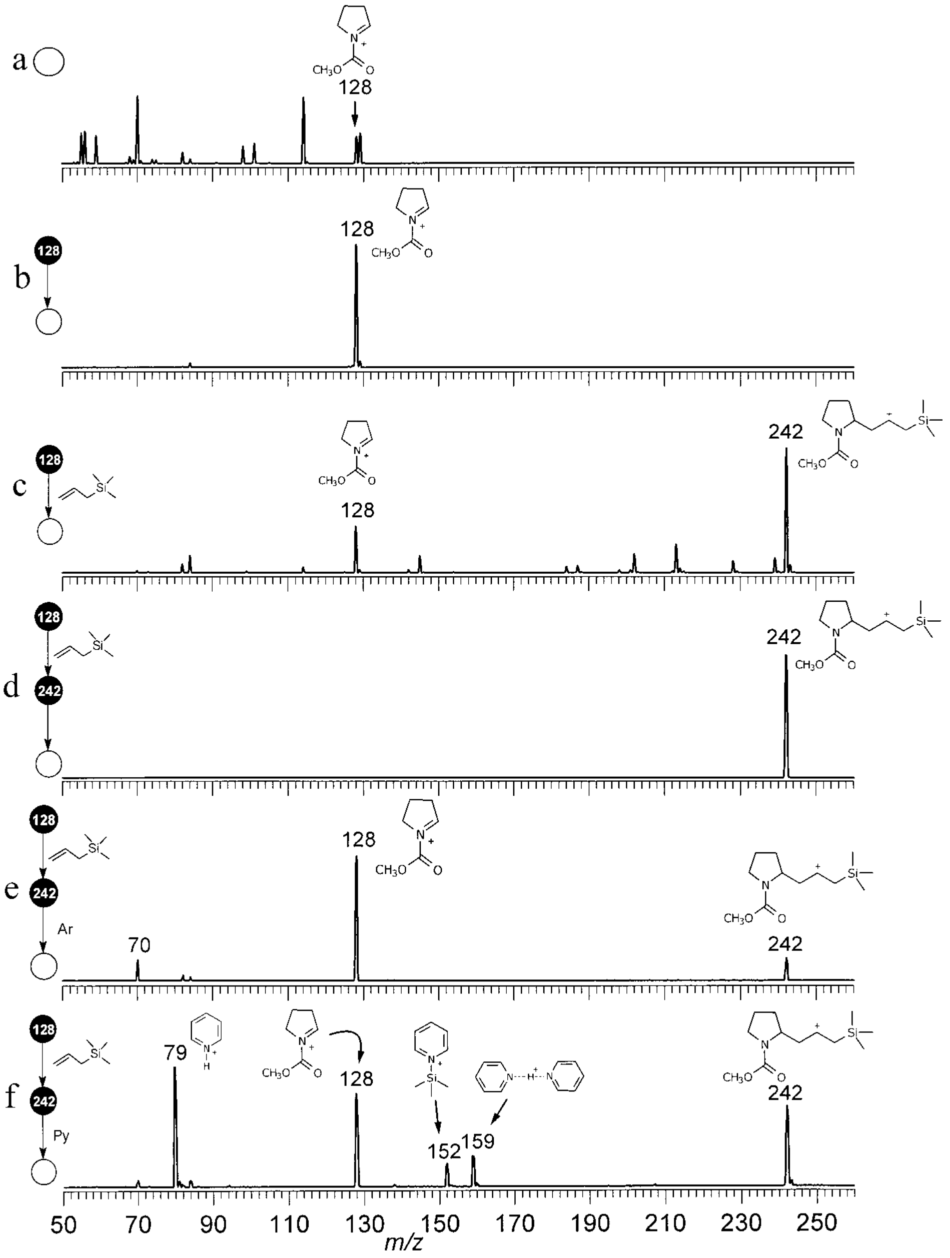

Figure 2. Series of MS^n ($n = 1, 3$) experiments used to form, isolate via mass-selection, and react **3c** with ATMS and to isolate, dissociate, and react the gaseous β-silyl cation product of *m/z* 242. (a) The 70 eV EI mass spectrum of *N*-methoxycarbonyl pyrrolidine. (b) Q1 isolation via mass-selection of **3c** of *m/z* 128. (c) Double-stage (MS^2) product ion mass spectrum for reactions of **3c** with ATMS. (d) Q3 isolation via mass-selection of the β-silyl cation product of *m/z* 242. Triple-stage (MS^3) product ion mass spectrum for (e) 15 eV CID of *m/z* 242 with argon and (f) for reactions of *m/z* 242 with pyridine.

212 from **2c**. Note in Figure 3 the greater yield of the $^+Si(CH_3)_3$ abstraction product of *m/z* 152, as compared with those of the product transfer products of *m/z* 80 and 159, and the absence of the CID product of *m/z* 98 (**2c**), which indicates high stability of *m/z* 212 toward Grob fragmentation.

(d) Relative Reactivity of Cyclic *N*-Acyliminium Ions. Figure 4 displays a combined product ion mass spectrum for reactions of **2a**, **2c**, **3a**, and **3c** with ATMS. Separate spectra for each reactant ion were collected by selecting a beam of these ions with close to the same absolute abundance and by reacting them with ATMS in q2 (Figure 4) using the same collision energy and low, nearly the same,[22]ATMS pressure so as to ensure the most similar and single collision conditions.[23] The spectrum of Figure 4 was then plotted using the absolute abundances of the reactant ions and those of their respective β-silyl cation products. For clarity, the superimposing peaks of the s-ATMS products were omitted.

Discussion

Order of Intrinsic Electrophilic Reactivity. From both the product ion mass spectra summarized in Table 1 and the comparative spectrum of Figure 4, and when considering the yield of stable β-silyl cations formed via ATMS addition, the following order of intrinsic electro-

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[22] The reaction conditions were not identical because pressures in q2 cannot be reproduced with high accuracy.

[23] Eberlin, M. N.; Kotiaho, T.; Shay, B. J.; Yang, S. S.; Cooks, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 2457.

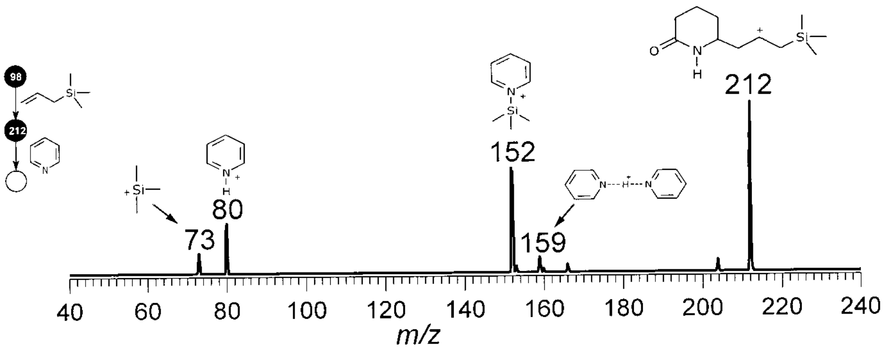


Figure 3. Triple-stage (MS^3) product ion mass spectrum for reactions with pyridine of the β-silyl cation of *m/z* 212 formed by ATMS addition to **2c**.

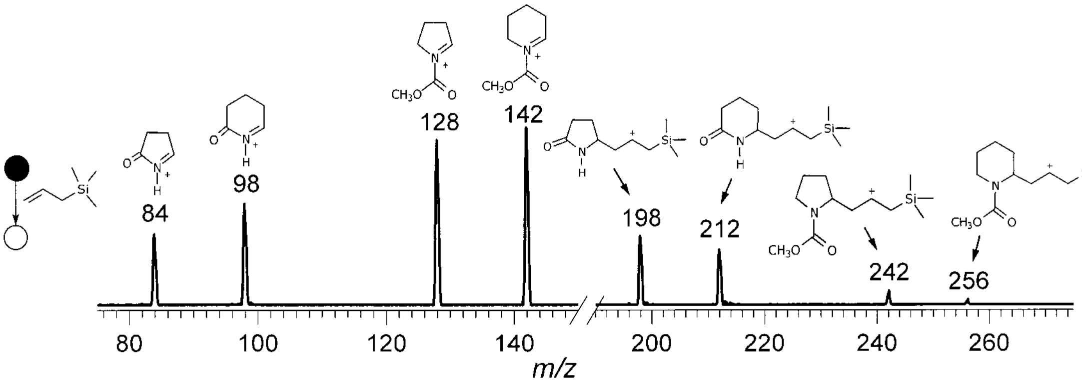
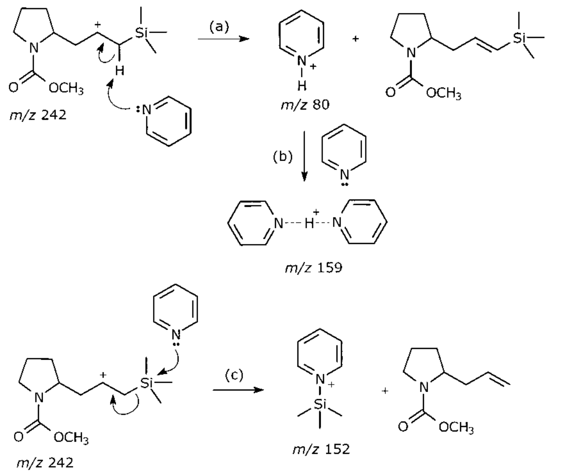
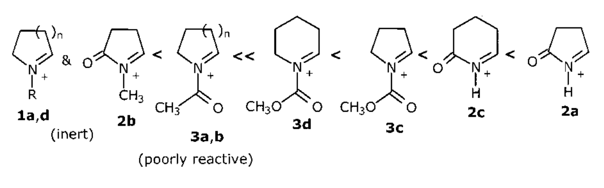


Figure 4. Combined double-stage (MS^2) product ion mass spectrum for reactions of **2a**, **2c**, **3c**, and **3d** with ATMS under nearly the same and single-collision reaction conditions. The superimposing peaks of the s-ATMS products have been omitted for clarity. Each individual spectra were corrected for dissociation of the reactant ion.

Scheme 3



philic reactivity of the cyclic iminium ions is derived:



N-Alkyliminium ions (**1**) are deactivated toward nucleophile addition except of those bearing highly polarized carbon−carbon double bonds. For *N*-alkyliminium ions, the C-2 charge is diminished owing to effective delocalization with the adjacent nitrogen,[3] and the lack of *N*-acyl groups also disfavors adduct formation because the reverse reaction, Grob fragmentation,[19] is facilitated by the electron-rich nitrogen atoms.[3]

Exocyclic *N*-acyl groups disfavor Grob fragmentation[19] of the β-silyl cation product and increase the ion's electrophilicity via resonance interaction with the nitrogen lone pair and an electron-attracting inductive effect, thus favoring ATMS addition. But facile rotation of the *N*-acyl bond (rotation barriers on the order of 10 kcal/mol or less[24]) likely minimizes considerably these effects; hence activation is minor and the *N*-$COCH_3$ iminium ions **3a** and **3b** are not very reactive toward ATMS addition (Table 1).

Ions **2a** and **2c** with endocyclic *N*-carbonyl groups are, however, locked in planar *s-trans* conformations that favor N−C=O cross conjugation and reduce cation stabilization by the nitrogen electron pair; hence ATMS addition at the more electrophilic C-2 occurs readily. For **2b**, however, the electron-donating *N*-CH_3 substituent seems able to provide enough cation stabilization so as to cancel the activation provided by the endocyclic *N*-carbonyl group. Hence, **2b** is inert toward ATMS addition (Table 1) reacting preferentially likely by hydride or methanide abstraction to form the s-ATMS products (Table 1). But, although *N*-CH_3 deactivation is expected, the inertness of the *N*-CH_3 ion **2b** toward ATMS addition is surprising, especially considering that its *N*-H analogue **2a** is the most reactive ion.

Exocyclic *N*-alkoxycarbonyl groups have also been found to be particularly effective in activating iminium ions toward addition of carbon nucleophiles.[3] Accordingly

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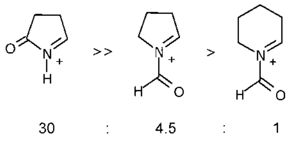
[24] Lamatsch, B.; Seebach, D.; Ha, T.-K. *Helv. Chim. Acta* **1992**, *75*, 10.

therefore, **3c** and **3d** are placed as the second pair of most reactive ions. The more electron-attracting *N*-CO_2CH_3 group increases the electron deficiency at C-2,[3] but it may also increase reaction rates for ATMS addition by strengthening the *N*-CO_2CH_3 bond, thus inhibiting *N*-CO_2CH_3 bond rotation as compared with the *N*-$COCH_3$ group of **3a** and **3b**. In accordance with this expectation, the calculations (see below) predict for **3c** (1.482 A) and **3d** (1.498 A) shorter N−COR bonds than those of **3a** (1.528 A) and **3b** (1.545 A).

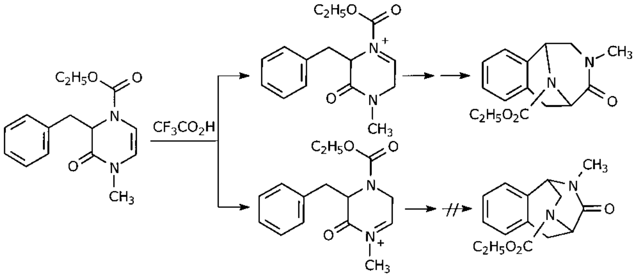
Five- versus Six-Membered Ring *N*-Acyliminium Ions. When the analogous five- and six-membered ring *N*-acyliminium ions are compared, **2a** versus **2c** and **3c** versus **3d**, the five-membered ring ions **2a** and **3c** are found to be more reactive toward ATMS addition (Figure 4). Under nearly the same single collision conditions, the five-membered ring ion **2a** of *m*/*z* 84 forms more of the β-silyl cation of *m*/*z* 198 than **2c** of *m*/*z* 98 forms *m*/*z* 212. Similarly, **3c** of *m*/*z* 128 forms more of *m*/*z* 242 than **3d** of *m*/*z* 142 forms *m*/*z* 256.

Gas-Phase versus Solution Reactivity. In solution, the reactivity of *N*-acyliminium ions toward nucleophiles, as measured by the overall reaction rate, depends on the rate-determining step:[3,4a] (i) formation of the *N*-acyliminium ion or (ii) the addition of the carbon nucleophile to the *N*-acyliminium ion. The order of gas-phase reactivity now measured for iminium ions toward ATMS addition, which should be affected only by their intrinsic eletrophilic reactivities, is fully compatible with orders of *overall* reactivity measured in solution.[3] In solution, the cyclic *N*-alkyliminium ions **1** are also the least reactive, often inert. The relative reactivity of gaseous *N*-acyliminium ions with endocyclic *N*-carbonyl, exocyclic *N*-alkoxycarbonyl, and exocyclic *N*-alkylcarbonyl groups, that is, **2a**,**c** > **3c**,**d** ≫ **3a**,**b**, is also fully compatible with orders of overall reactivity observed in solution,[3] and with ^{13}C NMR shifts observed for *N*-acyliminium ion salts.[3a,25] In the ^{13}C NMR spectrum, *N*-CH_3 by *N*-$COCH_3$ substitution leads to a downfield shift of the C-2 absorption of about 5 ppm and of a *N*-$COCH_3$ by a *N*-$CO_2C_2H_5$ group of about 1 ppm.[25] These downfield shifts indicate therefore higher electron deficiency on the eletrophilic C-2and hence greater electrophilicity for *N*-acyliminium ions as compared with *N*-alkyliminium ions, and for *N*-$CO_2C_2H_5$ iminium ions as compared with *N*-$COCH_3$ iminium ions.

Malmberg and Nyberg[26] formed *N*-acyliminium ions from α-methoxyamides and observed an order of reactivity toward arylation with 1,3,5-trimethoxybenzene that, when directly related to the ion's reactivities (see below), is also fully compatible with the order of intrinsic electrophilic reactivity with ATMS now measured for the gaseous *N*-acyliminium ions.

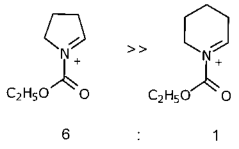


Scheme 4



The results of Kurihara and Mishima[27] for the intramolecular cyclization reactions summarized in Scheme 4 are also fully compatible with the high reactivity toward ATMS addition of the gaseous *N*-acyliminium ions **3c** and **3d** with exocyclic *N*-CO_2CH_3 groups and the inertness of the gaseous *N*-acyliminium ion **2b** with a *N*-CH_3 group.

In solution, five-membered ring *N*-acyliminium ions have also been reported to be, *overall*, more reactive than their six-membered ring analogues,[3] as already exemplified by the order of reactivity reported by Malmberg and Nyberg[26] (see above). Recently, competitive reactions with a silyl enol ether using equimolar amounts of the two 2-ethoxycarbamate precursors were found to yield the product arising from reaction with the five-membered exocyclic *N*-$CO_2C_2H_5$ ion (see below) in an amount six times greater than that from its six-membered ring analogue.[28] Accordingly, the reaction of titanium(IV) enolates of *N*-acyloxazolidin-2-ones with *N*-Boc five- and six-membered ring *N*-acyliminium ions revelead the same pattern.[29]



***β*-Silyl Cations.** The reaction of the β-silyl cations with pyridine (Figures 2f and 3) is used for structural characterization of the ions and also to investigate, for the first time, the intrinsic reactivity toward a nucleophile of these important but transient reaction intermediates. The reaction tested whether a nucleophile would abstract the $Si(CH_3)_3^+$ ion—the key step of α-amidoalkylation reactions (Scheme 1). The results exemplified in Figures 2f and 3 confirm the expectation since $Si(CH_3)_3^+$ abstraction by pyridine[21] is observed as a major reaction for all β-silyl cation intermediates, thus corroborating the proposed mechanism.[3] Proton transfer was also observed; hence this reaction may compete in solution with $Si(CH_3)_3^+$ abstraction depending on the properties of the β-silyl cation and the basic versus nucleophilic character of the nucleophile. But in solution, proton transfers (Scheme 3, pathway a) are fast, reversible reactions; thus the β-silyl cation can be rapidly re-formed and then irreversibly consumed by $Si(CH_3)_3^+$ abstraction.

Dissociation Behavior. The CID spectra of the gaseous β-silyl cations (Figure 2e) are also relevant when considering the mechanism proposed for the α-amidoalkylation reaction. Collision activation of the β-silyl cations is shown to preferentially reform the reactants,

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[25] (a) Würthwein, E.-U.; Kupfer, R.; Kaliba, C. *Angew. Chem. Suppl.* **1982**, 264. (b) Funk, W.; Hornig, K.; Moller, M. H.; Würthwein, E.-U. *Chem. Ber.* **1993**, *126*, 2069.

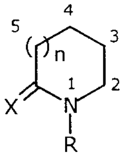
[26] Malmberg, M.; Nyberg, K. *Acta Chem. Scand. Ser. B* **1981**, *35*, 411.

[27] Kurihara, H.; Mishima, H. *Heterocycles* **1982**, *17*, 191.

[28] Alves, C. F. Ph.D. Thesis, State University of Campinas, Campinas, SP, Brazil, 1998.

[29] Pilli, R. A.; Böckelmann, M. A.; Alves, C. F. *J. Braz. Chem. Soc.* In press.

Table 2. Becke3LYP/6-311G(d,p) Charge Densities for the Iminium Ions 1−3

Ion	Charge[a]						
	N1	C-2	C-3	C-4	C-5	C=X ($X = H_2$, O)	*N*-R[b]
1a	0.018	**0.422**	0.131	0.103	--	0.324	--
1b	-0.299	**0.402**	0.124	0.097		0.310	0.365
1c	0.002	**0.396**	0.133	0.094	0.060	0.314	--
1d	-0.303	**0.375**	0.132	0.089	0.062	0.296	0.346
2a	0.001	**0.470**	0.145	0.178	--	0.206	--
2b	-0.330	**0.444**	0.134	0.193	--	0.169	0.388
2c	-0.022	**0.449**	0.129	0.115	0.129	0.203	--
3a	-0.364	**0.436**	0.141	0.102	--	0.315	0.368
3b	-0.380	**0.409**	0.151	0.093	0.063	0.303	0.359
3c	-0.365	**0.438**	0.139	0.095	--	0.337	0.354
3d	-0.382	**0.414**	0.148	0.092	0.056	0.326	0.345

[a] Charge densities for the hydrogens and oxygens were summed into those of the carbon atoms. [b] Total charge density for the substituent on nitrogen.

that is, to induce Grob fragmentation.[19] Dissociation to $Si(CH_3)_3^+$ fails to occur, and this finding therefore agrees with the proposal that $Si(CH_3)_3^+$ abstractions that form the final α-amidoalkylation product (Scheme 3c) are promoted by nucleophile attack.

Theoretical Calculations

Charge Distributions. As an approach to estimate the carbocation character of cyclic iminium ions, charge distributions were estimated by Becke3LYP/6-311G(d,p) calculations (Table 2). Roughly, one could expect that the higher the electron deficiency on C-2 (the site of nucleophilic attack), the higher the carbocation character and the higher the electrophilic reactivity of the iminium ion.

In *N*-alkyliminium ions with no electron-withdrawing *N*-acyl groups, the nitrogen lone pair is more available for cation stabilization that diminishes considerably the electron defficiency at C-2; hence, as expected, ions **1** display the lowest C-2 positive charges (and consequently for **1a** and **1c** the highest N charges). The parent five-membered ring *N*-alkyliminium ion **1a** displays a C-2 charge of +0.422. Both a *N*-CH_3 group (**1b**, +0.402) and ring expansion that adds an electron-donating methylene group to the ring (**1c**, +0.396) favor cation stabilization and decrease, as expected, the C-2 charges. For **1d**, an ion that bears both a *N*-CH_3 and an extra methylene ring group, the C-2 charge is depleted even further to +0.375.

The *N*-acyliminium ion **2a** bears an endocyclic, coplanar, *s-trans* locked electron-attracting *N*-carbonyl group that disfavors by cross conjugation cation stabilization by the nitrogen; hence, **2a** displays, in contrast with ions **1**, the highest C-2 charge (+0.470).[30] Note also that, compared to **1a**, the electron-withdrawing carbonyl group in **2a** replaces in the ring an electron-donating methylene group. Both a *N*-CH_3 and the extra methylene group in the ring (that is five- to six-membered ring expansion) decrease to similar extents the C-2 charges of **2b** (+0.444) and **2c** (+0.449), compared with **2a** (+0.470). The *N*-acyliminium ion **3a**, with an exocyclic *N*-$COCH_3$ group in its (unlocked) *s-cis* conformation, also displays increased C-2 charge (+0.436), compared with **1a**, but this increase is not as pronounced as that observed for **2a** (+0.470). Note that the electron-donating methylene groups in the ring of **3a** (compared to **2a**) should minimize, as for **2b**, the electron-attracting effect of the exocyclic *N*-$COCH_3$ group.

When the C-2 charge-*increasing* effects (higher electrophilicity) of the exocyclic *N*-$COCH_3$ and *N*-CO_2CH_3 groups are compared, for both the five- and six-membered ring ions, a slight but consistently more pronounced effect for *N*-CO_2CH_3 is observed: **3a** (+0.436) versus **3c** (+0.438)

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[30] A substantial increase in the C-2 charge has also been predicted by ab initio calculations for the *N*-acyliminium ion $HC(=O)N^+=CH_2$ (+0.740) as compared with that of $H_2N^+=CH_2$ (+0.686), see ref 24.

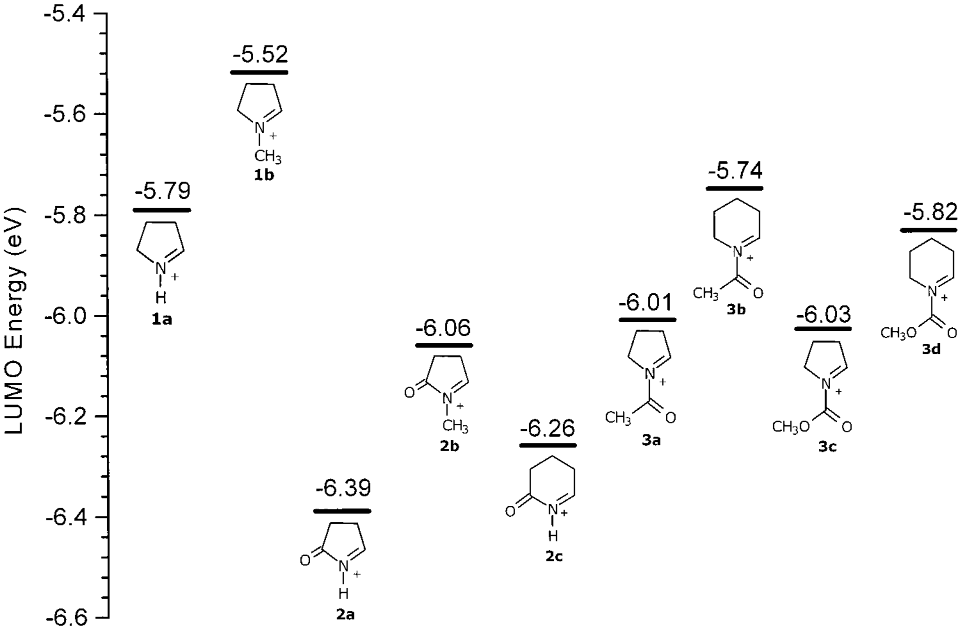

Figure 5. AM1 LUMO energies of the cyclic *N*-alkyl- and *N*-acyliminium ions.

and **3b** (+0.409) versus **3d** (+0.414). The C-2 charges of the five-membered ring ions with one less electron-donating cation-stabilizing methylene group are also consistently more positive than those of the six-membered ring analogues: **3a** > **3b** and **3c** > **3d**.

LUMO Energies. Figure 5 compares the LUMO energies of most of the *N*-alkyliminium and *N*-acyliminium ions investigated. Because we attempt to compare eletrophilic reactivities, LUMO energies should be considered for the frontier orbital interactions; hence the lower the LUMO energy the higher the ion's electrophilic reactivity. The prototype five-membered ring *N*-alkyliminium ion **1a** (−5.79 eV) and its *N*-CH_3 analogue **1b** (−5.52 eV) display the highest LUMO energies; hence, they are predicted (and observed) to display the lowest electrophilic reactivities. In contrast, the prototype five- and six-membered ring *N*-acyliminium ions **2a** (−6.39 eV) and **2c** (−6.26 eV), with *s-trans* locked endocyclic *N*-carbonyl groups, display the lowest LUMO energies, and they are therefore predicted (and observed) to be the most reactive. The five- and six-membered ring *N*-acyliminium ions with exocyclic *N*-$COCH_3$ [**3a** (−6.01) and **3b** (−5.74)] and *N*-CO_2CH_3 [**3c** (−6.03 eV) and **3d** (−5.82 eV)] groups, when calculated in their most favored (but unlocked) *s-cis* conformations, also display diminished LUMO energies, but the effects of their exocyclic *N*-acyl groups are much less intense. Five- to six-membered ring expansion increases the LUMO energy of *N*-acyliminium ions: **2a** (−6.39 eV) versus **2c** (−6.26 eV), **3a** (−6.01 eV) versus **3b** (−5.74 eV), and **3c** (−6.03 eV) versus **3d** (−5.82 eV). An even more pronounced increase in LUMO energy occurs via *N*-H by *N*-CH_3 replacement in the five-membered ring *N*-acyliminium ions with endocyclic *N*-carbonyl groups: **2a** (−6.39 eV) versus **2b** (−6.06 eV).

Reaction Enthalpies. Figure 6 summarizes the enthalpies calculated at the Becke3LYP/6-311G(d,p) level[31,32] for addition of ATMS to most of the cyclic iminium ions studied. Interestingly, ATMS additions to **1a** and **1b** are predicted to be *endothermic* and therefore thermodynamically unfavorable. Hence, Grob fragmentation[19] of any transient *β*-silyl cation product of **1a** and **1b**, and likely of most simple iminium ions, must be exothermic, fast, and complete, as predicted.[3] In contrast, ATMS addition to the *N*-acyliminium ions is predicted to be exothermic and therefore thermodynamically favorable.

When ATMS addition to the analogous five- and six-membered ring ions **2a** (−15.9 kcal/mol) and **2c** (−11.3 kcal/mol) are compared, that for **2c** is considerably less exothermic. When ATMS addition to **2a** (−15.9 kcal/mol) is compared with that of its *N*-CH_3 analogue **2b** (−7.3 kcal/mol), an even more pronounced reduction in the reaction exothermicity is observed.

Energy Thresholds for Dissociation and Enthapies for Reactions with Pyridine. Figure 7 summarizes the enthalpies calculated at the Becke3LYP/6-311G(d,p) level[31] for dissociation (Scheme 2) and reaction with pyridine (Scheme 3) of the *β*-silyl cation formed by ATMS addition to **3c**. As experimentally observed (Figure 2e), Grob fragmentation (+17.5 kcal/mol) that re-forms **3c** is much more favored than the dissociation that yields $Si(CH_3)_3^+$ (+39.2 kcal/mol). In reactions with pyridine (Figure 2f), proton (−3.7 kcal/mol) and $Si(CH_3)_3^+$ abstraction (−23.5 kcal/mol) are both exothermic and therefore energetically favored, with a greater thermodynamic preference for $Si(CH_3)_3^+$ abstraction. This preference, which is perhaps masked in Figure 2f by concomitant proton transfer from the *m*/*z* 128 CID product, is clearly seen in Figure 3.

Concluding Remarks

Using MS^2 and MS^3 experiments, five- and six-membered ring *N*-alkyl- and *N*-acyliminium ions were

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[31] Exocyclic *N*-acyliminium ions were calculated at their most stable *s-cis* conformation, see: Kupfer, R.; Würthwein, E.-U.; Nagel, M.; Allmann, R. *Chem. Ber.* **1985**, *118*, 643.

[32] The Becke3LYP/6-311G(d, p) energies (in hartrees) for the ions and their ATMS adducts are **1a** (−211.81387, −738.49502), **1b** (−251.14649, −777.82764), **2a** (−285.82429, −812.50544), **2b** (−325.15767, −851.83882), **2c** (−851.83751) **3a** (−364.48305, −891.16420), and **3c** (−439.73422, −966.44334) and of ATMS (−526.68114). The energies for the additional species shown in Figure 7 are pyridine (−248.34687), *N*-protonated pyridine (−248.71789), [pyridine + $Si(CH_3)_3^+$] (−657.49107), and [**3c** + ATMS − H^+] (−966.07813), [**3c** + ATMS − $Si(CH_3)_3^+$] (−557.33662).

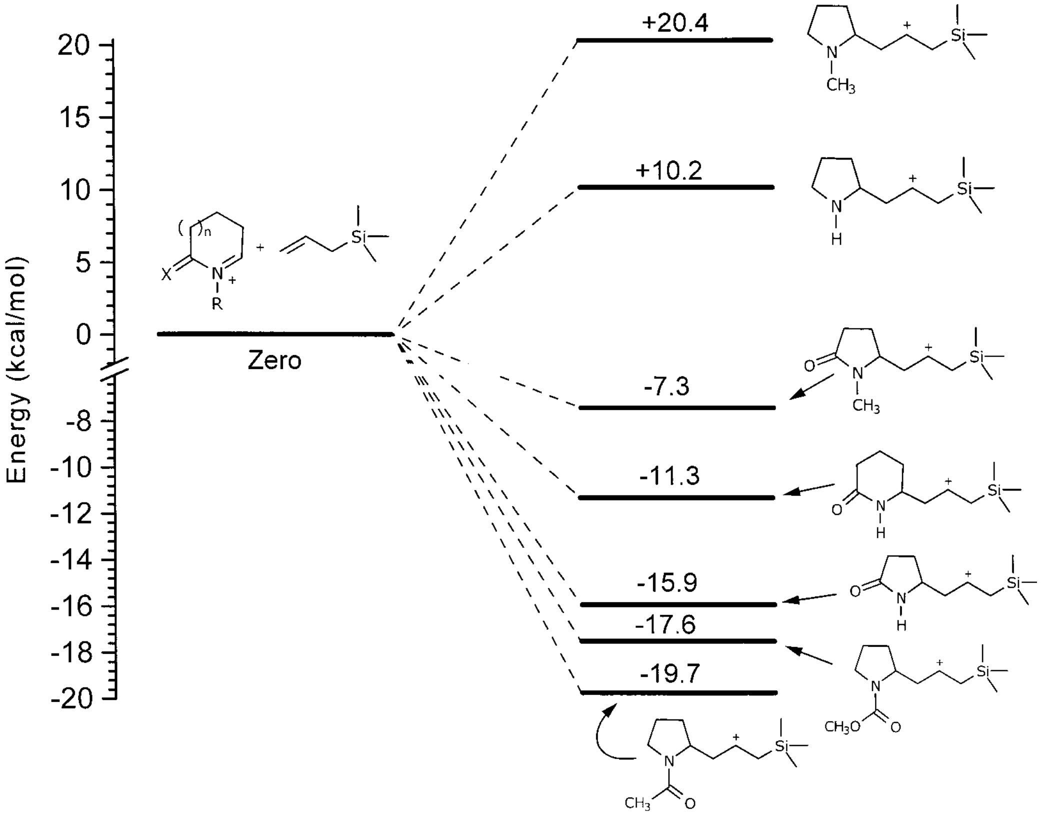

Figure 6. Becke3LYP/6-311G(d,p) reaction enthalpies[32] for addition of ATMS to cyclic *N*-alkyl- and *N*-acyliminium ions.

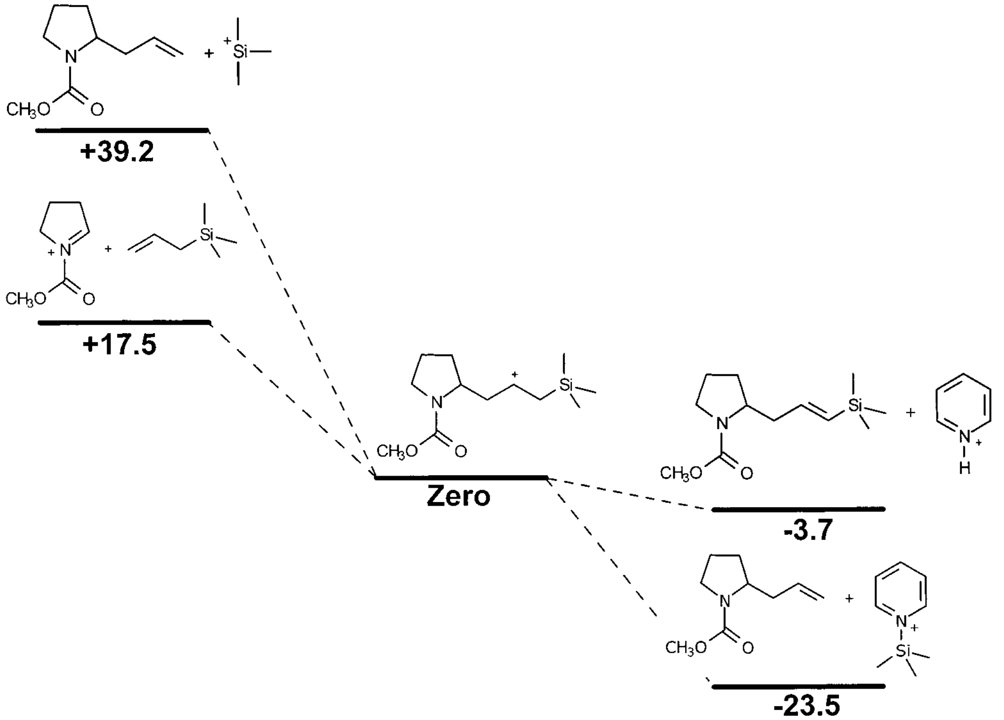

Figure 7. Becke3LYP/6-311G(d,p) enthalpies[32] for dissociation and reactions with neutral pyridine of the *β*-silyl cation formed by ATMS addition to **3c**. The neutral pyridine reactant has been omitted for clarity.

formed and isolated, and their gas-phase intrinsic reactivity toward ATMS addition was systematically investigated. An order of electrophilic reactivity was derived and, when compared with results in solution, the agreement is remarkable. Similar to the behavior of the ions in solution, the cyclic *N*-alkyliminium ions **1**, lacking *N*-acyl activation, are found to be inert toward ATMS addition. Accordingly, Becke3LYP/6-311G(d,p) calculations show that **1** display the least pronounced carbocation character (C-2 charges) and highest LUMO energies, and their ATMS addition reactions are *endothermic*. Hence, *β*-silyl cations formed by ATMS addition to **1** are likely to be metastable with respect to Grob fragmentation. The *N*-acyliminium ions **2a** and **2c**, with endocyclic *N*-carbonyl groups, are locked in *s-trans* conformations that favors cross conjugation and makes their nitrogen lone pairs less available for cation stabilization, and, accordingly, they are the most reactive toward ATMS addition. The *N*-acyliminium ions **3c** and **3d** with *unlocked* exocyclic *N*-CO_2CH_3 groups are the second pair of most reactive ions. Reactions in solution have shown, accordingly, similar *overall* reactivity orders for cyclic *N*-acyliminium ions. The calculations also show that the *N*-acyliminium ions **2** and **3**, particularly **2** with endocyclic *s-trans* locked *N*-carbonyl groups, display as compared to *N*-alkyliminium ions more pronounced carbocation character, as demonstrated by their highest positive C-2 charges, lowest LUMO energies, and more exothermic ATMS addition reactions, which reflect the greater stability of their adducts toward Grob fragmentation.

Five-membered ring *N*-acyliminium ions are found to be more reactive toward ATMS addition than their six-membered ring analogues, that is, **2a** > **2c** and **3c** > **3d**. This finding is in accordance with both solution results and theoretical predictions: ring expansion by the addition of an electron-donating methylene group decreases the C-2 positive charge, raises the LUMO energy, and makes ATMS addition less exothermic. In contrast with the higher reactivity of **2a**, its *N*-methyl analogue **2b** is inert toward ATMS addition. Accounting for this inertness, the calculations indicate a strong deactivating effect of endocyclic *N*-acyliminium ions caused by an *N*-methyl group as it, more pronouncedly than a methylene group added to the ring, diminishes the C-2 charge, increases the LUMO energy, and makes ATMS addition less exothermic.

The five- and six-membered ring iminium ions **3a** and **3b**, with exocyclic *N*-$COCH_3$ groups, are not very reactive toward ATMS addition. Although the calculations show that ATMS additions to these ions are as much exothermic as those of the most reactive ions, the exocyclic *N*-$COCH_3$ group, even in its most favored (but unlocked) *s-cis* conformation, is less effective in enhancing the carbocation character (C-2 charges) and in lowering the LUMO energies. In addition, it is likely that the low-energy barrier for rotation of the *N*-$COCH_3$ bond (on the order of 10 kcal/mol or less[24]) further and pronouncedly attenuates these effects while kinetically disfavoring ATMS addition to exocyclic *N*-acyliminium ions.

Therefore, the present results indicate that, toward nucleophile addition and in the absence of major solvent or counterion effects, *N*-acyliminium ions with five-membered rings and with endocyclic *N*-carbonyl or exocyclic *N*-alkoxycarbonyl groups, followed by their six-membered ring analogues, are *the most reactive N*-acyliminium ions.

For the first time, the transient intermediates of a Mannich-type condensation reaction were isolated—the β-silyl cations of ATMS addition to *N*-acyliminium ions—and their gas-phase behavior toward dissociation and nucleophile attack investigated. The β-silyl cations dissociate preferentially by Grob fragmentation (retro-addition) and react to variable extents with pyridine (a reference nucleophile) both by proton transfer and $Si(CH_3)_3^+$ abstraction—the final and key step postulated in the α-amidoalkylation mechanism.

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