
Cyclization Reactions of Acylium and Thioacylium Ions with Isocyanates and Isothiocyanates: Gas Phase Synthesis of 3,4-Dihydro-2,4-Dioxo-2H-1,3,5-Oxadiazinium Ions

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Gas-phase reactions of several acylium and thioacylium ions, that is $\text{H}_2\text{C}=\text{N}-\text{C}^+=\text{O}$, $\text{H}_2\text{C}=\text{N}-\text{C}^+=\text{S}$, $\text{O}=\text{C}=\text{N}-\text{C}^+=\text{O}$, $\text{S}=\text{C}=\text{N}-\text{C}^+=\text{O}$, $\text{H}_3\text{C}-\text{C}^+=\text{O}$, and $(\text{CH}_3)_2\text{N}-\text{C}^+=\text{O}$, with both a model isocyanate and isothiocyanate, that is, $\text{C}_2\text{H}_5-\text{N}=\text{C}=\text{O}$ and $\text{C}_2\text{H}_5-\text{N}=\text{C}=\text{S}$, were investigated using tandem-in-space pentaquadrupole mass spectrometry. In these reactions, the formation of mono- and double-addition products is observed concurrently with proton transfer products. The double-addition products are far more favored in reactions with ethyl isocyanate, whereas the reactions with ethyl isothiocyanate form, preferentially, either the mono-addition product or proton transfer products, or both. Retro-addition dominates the low-energy collision-induced dissociation of the mono- and double-addition products with reformation of the corresponding reactant ions. Ab initio calculations at Becke3LYP//6-311 + G(d,p) level indicate that cyclization is favored for the double-addition products and that products equivalent to those synthesized in solution, that is, of 3,4-dihydro-2,4-dioxo-2H-1,3,5-oxadiazinium ions and sulfur analogs, are formed. (J Am Soc Mass Spectrom 2005, 16, 1602–1607) © 2005 American Society for Mass Spectrometry

Tandem mass spectrometry [1–3] (MS^n) provides not only a means to perform gas-phase ion/molecule reactions with isolated and mass-selected ions under well-defined conditions but also the on-line structural analysis of each product ion. MS^n constitutes, therefore, a refined tool to perform elegant studies of the inherent properties, reactivity, and structures of gaseous ions with molecules of many classes [1–9]. MS^n experiments performed in this solvent- and counterion-free environment has been also of fundamental importance to understand and elucidate reaction mechanisms and to draw parallels to condensed-phase reactivity [4–19]. Tandem mass spectrometers also provide minute but very efficient synthetic laboratories [20–22] with some attractive possibilities for product collection such as ion soft-landing [23].

We have observed that acylium ions, a common class

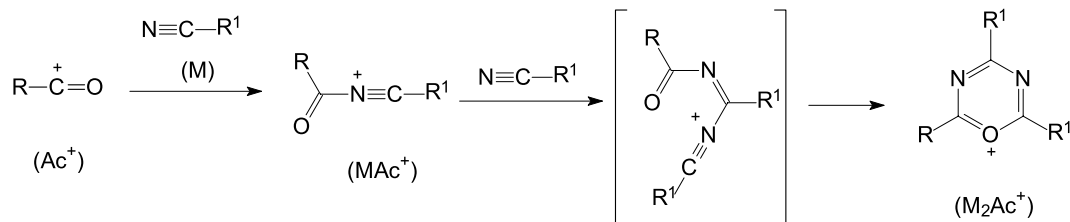
of gaseous ions, react promptly and diversely with many classes of compounds including acetals [24, 25], epoxydes, [26] α -hydroxi-ketones, [27], dienes, [28] and α,β -unsaturated ketones [29]. Recently, we reported that acylium ions also react readily with nitriles (M) via double nitrile addition followed by cyclization (Scheme 1) to form, via the intermediacy of mono-addition products (MAc^+), the aromatic 1,3,5-oxadiazinium ions (M_2Ac^+) [30].

Acylium ions are also important species in solution playing a fundamental role in the well-known and industrially relevant Friedel-Crafts acylation reaction [31]. They are also useful intermediates in the condensed-phase synthesis of many heterocycles via reactions with cyanamides, carbodiimides, alkenes, alkynes, and nitriles [32]. Solvated acylium ions were also found to react with alkyl isocyanates to yield unique double-addition cyclic products, namely, 3,4-dihydro-2,4-dioxo-2H-1,3,5-oxadiazinium salts in moderate yields [33].

Therefore, owing to the rich and useful reactivity exhibited by acylium ions in both the condensed and gas phases, and to our continuous interest in exploring

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Scheme 1

ion reactivities and the synthetic and analytical applications of their gas-phase reactions, herein we investigated, using tandem-in-space pentaquadrupole mass spectrometry, [7] the intrinsic reactivity of gaseous, solvent-, and counter-ion free acylium and thioacylium ions toward isocyanates and isothiocyanates.

Experimental

Chemical reagents were purchased from Aldrich (Milwaukee, WI) and used without further purification. Double-stage (MS^2) and triple-stage (MS^3) mass spectrometry experiments were performed with an Extrel (Pittsburgh, PA) pentaquadrupole ($Q_1q_2Q_3q_4Q_5$) mass spectrometer [34]. The following precursors were used to generate the reactant ions in the ion source via 70 eV electron ionization: $H_2C=N-C^+=O$ (ethyl isocyanate), $H_2C=N-C^+=S$ (ethyl isothiocyanate), $O=C=N-C^+=O$ (ethoxycarbonyl isocyanate), $S=C=N-C^+=O$ (ethoxycarbonyl isothiocyanate), $H_3C-C^+=O$ (methyl phenyl ketone), $(CH_3)_2N-C^+=O$ (tetramethyl urea). For the MS^2 experiments, the ion of interest was mass-selected in Q_1 and reacted in q_2 with the neutral isocyanate or isothiocyanate. Ion translational energies were set to ~ 1 eV, as calibrated by the m/z 39:41 ratio in neutral ethylene/ionized ethylene reactions [35]. To record the

product ion mass spectra, Q_5 was scanned while operating Q_3 in the broadband rf-only mode. Multiple collision conditions, which caused typical beam attenuation of 50 to 70%, were used in q_2 to increase reaction yields and to promote collisional quenching of both the reactant and product ions [7]. For the MS^3 experiments, [36] the products formed in q_2 were mass-selected in Q_3 and further dissociated by 15 eV collision energy with argon in q_4 while scanning Q_5 . The 15 eV collision energy was measured by the voltage difference between the ion source and the collision quadrupoles. The pressures in each mass spectrometer sector were typically: 2×10^{-6} (ion source), $8 - 10^{-6}$ (q_2), and 8×10^{-5} (q_4) torr.

Optimized geometries and energies of idealized conformations were obtained by theoretical calculations without symmetry constraints using Becke3LYP [37–39] DFT/HF hybrid functionals and 6-311 + G(d,p) basis sets as implemented in Gaussian 98 [40]. These structures are available from the authors upon request.

Results and Discussion

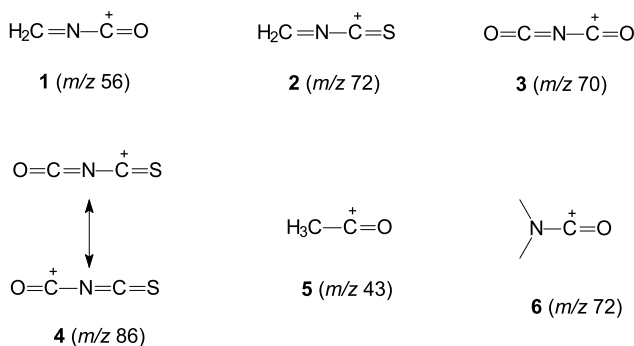
Table 1 summarizes the product ion mass spectra collected for the reactions of the acylium and thioacylium ions 1–6 (Ac^+) (Scheme 2) with both ethyl isocyanate 7 and ethyl isothiocyanate 8 (M) (Scheme 3) selected as model compounds. Additionally, Figure 1 displays, as an illustrative example, the product ion mass spectrum for the reaction of acylium ion 1 with isocyanate 7.

In general and under the multiple-collision conditions employed in the rf-only quadrupole collision cell, two major and competing reactions occur (Scheme 4): (i) proton transfer to the neutral (M) either from the

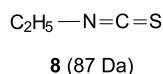
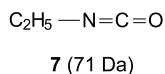
Table 1. Summary of the product ion mass spectra for reactions of the acylium and thioacylium ions 1–6 (Ac^+) with both ethyl isocyanate 7 and ethyl isothiocyanate 8

M	Ac^+	MAc^+ m/z (rel. intensity)	M_2Ac^+ m/z (rel. intensity)	$(M_2H^+), (MH^+)$ m/z (rel. intensity)
7	1	127 (7)	198 (100)	143 (20), 72 (13)
	2	a	214 (0)	a
	3	141 (13)	212 (100)	143 (7), 72 (42)
	4	157 (17)	228 (100)	143 (2), 72 (5)
	5	114 (52)	185 (44)	143 (100), 72 (2)
	6	a	214 (8)	a
8	1	143 (0)	230 (0)	175 (0), 88 (100)
	2	159 (100)	246 (5)	175 (65), 88 (14)
	3	157 (18)	244 (0)	175 (32), 88 (100)
	4	173 (0)	260 (0)	175 (0), 88 (100)
	5	130 (0)	217 (0)	175 (0), 88 (100)
	6	159 (100)	246 (2)	175 (90), 88 (10)

^aIn reactions of 2 and 6 with ethyl isocyanate 7, the following ions are isobaric (the same m/z ratio) and therefore could not be distinguished: (i) the mono-addition product MAc^+ and the proton-bound dimer M_2H^+ (m/z 143); and (ii) the reactant ion (2 or 6) and the protonated neutral MH^+ (m/z 72).



Scheme 2



Scheme 3

reactant ion Ac^+ or its products; and (ii) mono- (MAc^+) and double-addition (M_2Ac^+) products. For instance, in Figure 1 the mono- and double-addition adducts are those of m/z 127 and 198, respectively, whereas the products of m/z 72 (MH^+) and 143 (M_2H^+) arise by proton transfer. Although the structure of the double-addition product (M_2Ac^+) may be either acyclic or cyclic, ab initio calculations indicate that the cyclic structures presented in Scheme 4 are far more stable (see below). Note that these cyclic structures are equivalent to those synthesized in solution [33] and analogous to those observed for the double nitrile addition products of acylium ions (Scheme 1) [30].

The data of Table 1 reveal that ethyl isocyanate 7 reacts with 1, 3, and 4 to yield mainly the double-addition product M_2Ac^+ . The acetyl cation 5 also reacts with 7 to form M_2Ac^+ to some extent, but this ion is the only one that provides greater yields of both the proton transfer products MH^+ and M_2H^+ and the mono-adduct MAc^+ . In reactions of ethyl isocyanate 7 with 2 and 6, the product ions MAc^+ and M_2H^+ (m/z 143), as well as the reactant cations (2 or 6) and MH^+ (m/z 72), are isobaric and thus could not be distinguished. Furthermore, none (2) or little (6) of the double-addition product M_2Ac^+ (m/z 214) is formed in these reactions. With the sulfur analog 8, ethyl isothiocyanate, none (1, 3, 4, and 5) or little (2 and 6) of M_2Ac^+ is formed; 2 and 6 yield mainly MAc^+ whereas 1, 3, and 5 form predominantly MH^+ and M_2H^+ .

The contrasting product distributions verified in these reactions are likely influenced by the proton affinity (PA) of the neutral compound M as well as the gas-phase acidity of the reactant ion Ac^+ . For instance, proton-transfer products are preferentially formed with the model ethyl isothiocyanate 8 likely because of its greater proton affinity than that of ethyl isocyanate 7. This assumption is supported by reference proton affinity data [41] showing that PA of methyl isothiocyanate ($799.2 \text{ kJ}\cdot\text{mol}^{-1}$), the lower homologue of 8, is considerably greater than that of methyl isocyanate

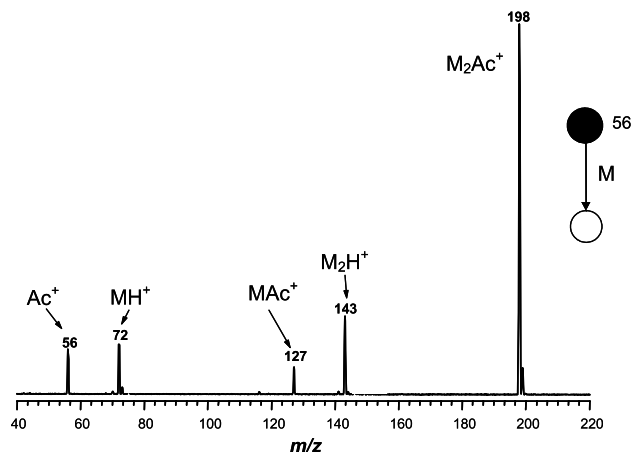


Figure 1. Product-ion mass spectrum for the reaction of the acylium ion 1 (Ac^+) with ethyl isocyanate 7 (M).

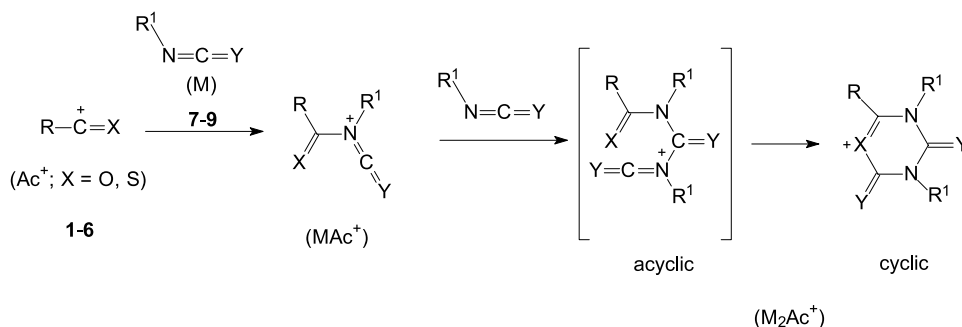
($764.4 \text{ kJ}\cdot\text{mol}^{-1}$), the lower homologue of 7. For reactant ions, the acetyl cation 5 (protonated ketene) shows the greatest tendency to react by proton transfer owing to its high gas-phase acidity, the highest among the ions investigated [7].

CID Experiments

CID experiments were performed in trying to obtain structural information for products MAc^+ and M_2Ac^+ . As an example, Figure 2 shows the sequential product ion mass spectra (MS^3) of the mono- and double-addition products from the reaction of 1 with 7. Both M_2Ac^+ of m/z 198 and MAc^+ of m/z 127 dissociate by retro-addition, that is, M_2Ac^+ dissociates to MAc^+ whereas MAc^+ dissociates to Ac^+ .

The $[\text{O}=\text{C}=\text{N}-\text{C}=\text{S}]^+$ Ion

The singly charged acylium-thioacylium ion 4, that is $[\text{O}=\text{C}=\text{N}=\text{C}=\text{S}]^+$, represents a special and interesting case since its initial addition to neutrals 7 or 8 may occur either via its C=O or C=S charge sites (Scheme 5), or via both sites, with the formation of either 10a or 10b, and either acyclic (11a or 11b) or cyclic (12a or 12b) double-addition products. However, as these adducts dissociate only by retro-addition (MS^3 data not shown),



Scheme 4

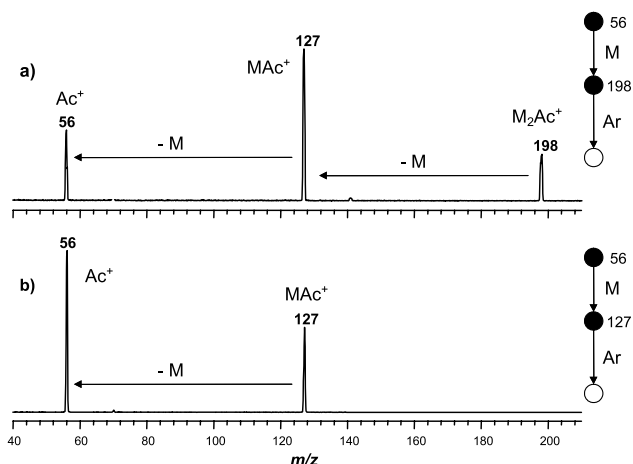


Figure 2. Sequential product ion mass spectra for (a) M_2Ac^+ and (b) MAc^+ formed in the reaction of ethyl isocyanate **7** (M) with acylium ion **1**.

no information about which isomeric product is preferentially formed is provided; hence we had to rely on theoretical predictions (see below).

Ab Initio Calculations: Reaction Enthalpies

Ab initio calculations were performed to compare the thermodynamic stabilities of the addition products. **Figure 3** shows, as an example, the energy diagram calculated for the reaction of the singly charged acylium-thioacylium ion $[O=C=N=C=S]^+$ (**4**) with **7**. Both mono-addition products **10a** and **10b** (Scheme 5) are 70.3 and 100.0 kJ mol^{-1} more stable in respect to the initial reagents. Therefore, the initial addition of **7** to the $C=S$ charge site of **4** is 29.7 kJ mol^{-1} more exothermic than $C=O$ addition. The calculations also show that the acyclic double-addition product **11a** is 30.5 kJ mol^{-1} more stable than its precursor **10a** whereas the alternative acyclic double-addition adduct **11b** is, curiously, found to be unstable at this level of calculation. In

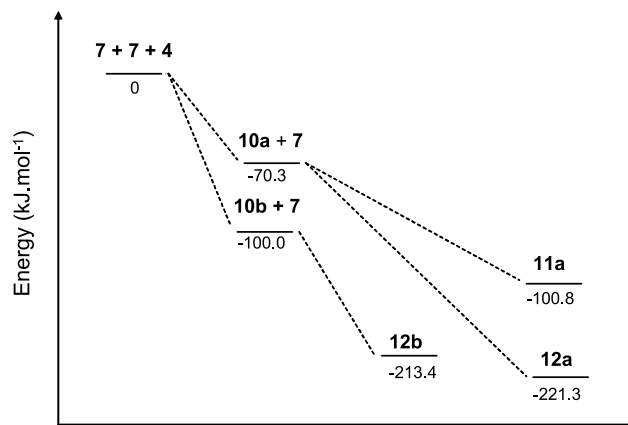
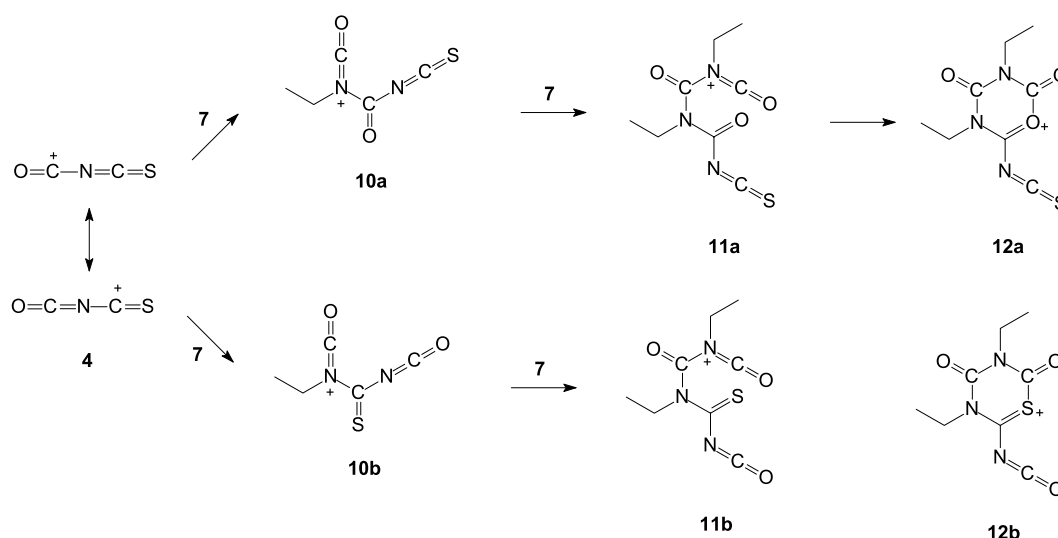


Figure 3. Energy diagram calculated at Becke3LYP//6-311 + G(d,p) level for consecutive additions of ethyl isocyanate (**7**) to the singly charged acylium-thioacylium ion **4**, that is, $[O=C=N=C=S]^+$. Energies are given in kJ mol^{-1} . The acyclic double-addition product is found to be unstable at this level of calculation. See Scheme 5 for the corresponding structures.

addition, the cyclic double-addition products **12a** and **12b** are predicted to be by far the most stable products, formed via very exothermic reactions: -221.3 and -213.4 kJ mol^{-1} , respectively. Furthermore, the small difference in energy for these double-addition cyclic products, of just 7.9 kJ mol^{-1} , indicates that both **12a** and **12b** are concomitantly formed in the gas phase.

Conclusions

Acylium and thioacylium ions were reacted with ethyl isocyanate and ethyl isothiocyanate in the gas-phase. Owing likely to its lower proton affinity that disfavors proton transfer reactions, double addition products are formed to great extents in reactions with the neutral ethyl isocyanate. In reactions with the neutral ethyl isothiocyanate, either the mono-adduct or proton transfer products, or both, dominate. CID experiments reveal that the mono- and double-addition products dissociate



Scheme 5

exclusively by retro-addition. Ab initio calculations at the Becke3LYP//6-311 + G(d,p) level indicate that, similarly to what is observed in solution, cyclization is greatly favored for the double-addition products in the gas-phase, and that 3,4-dihydro-2,4-dioxo-2H-1,3,5-oxadiazinium ions are formed.

Acknowledgments

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