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Acetamide enolate: formation, reactivity, and proton affinity

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Abstract

Acetamide enolate (**1**) was selectively prepared in a Fourier transform mass spectrometer and a variable temperature flowing afterglow apparatus by the fluoride-induced desilylation of 2-(trimethylsilyl)acetamide. Its reactivity, proton affinity, and collision-induced dissociation spectra were explored and contrasted to its isomeric amidate anion (**2**). Since **1** and **2** are ambident nucleophiles, their reactivity with perfluoropropylene and perfluorobenzene was investigated. The unimolecular isomerization of **1** to **2** also was examined at temperatures up to 300 °C. No rearrangement was observed under these conditions indicating that the activation barrier is at least 32 kcal mol^{-1}. Structures and energies of acetamide, its conjugate bases, and the transition structure interconverting **1** and **2** were computed using a variety of ab initio and density functional theory approaches. (Int J Mass Spectrom 210/211 (2001) 153–163) © 2001 Elsevier Science B.V.

Keywords: Acetamide enolate; Ambident nucleophiles; Ab initio calculations; CID; FTMS

1. Introduction

Condensation reactions of enolate ions leading to the formation of carbon–carbon bonds have been extensively investigated and are extremely important processes in organic synthesis and biological systems [1–7]. Deprotonated amides at carbon (amide enolates) are a particularly significant subset of these species not only because of their stability and extensive use in asymmetric syntheses [6–8] but they also have been implicated in the racemization of amino acids in polypeptides and cellular proteins during the aging process [9–11]. The simplest enolate of this type is the conjugate base of acetamide ($^{-}CH_2CONH_2$, **1**), and it has been the subject of ab initio and density functional theory calculations [12–14]. This ion also has been examined in the development of a theoretical model for amino acid racemization [12], but it has not been characterized experimentally. In this article we describe the gas-phase preparation, reactivity, and proton affinity of acetamide enolate, provide comparisons with the isomeric amidate ion (CH_3CONH^{-}, **2**), and compare the results to high-level ab initio and density functional theory computations.

2. Experimental

2-(Trimethylsilyl)acetamide was prepared by passing gaseous ammonia through trimethylsilylketene

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Dedicated to Nico M.M. Nibbering on the occasion of his retirement and in honor of his extensive contributions in mass spectrometry.

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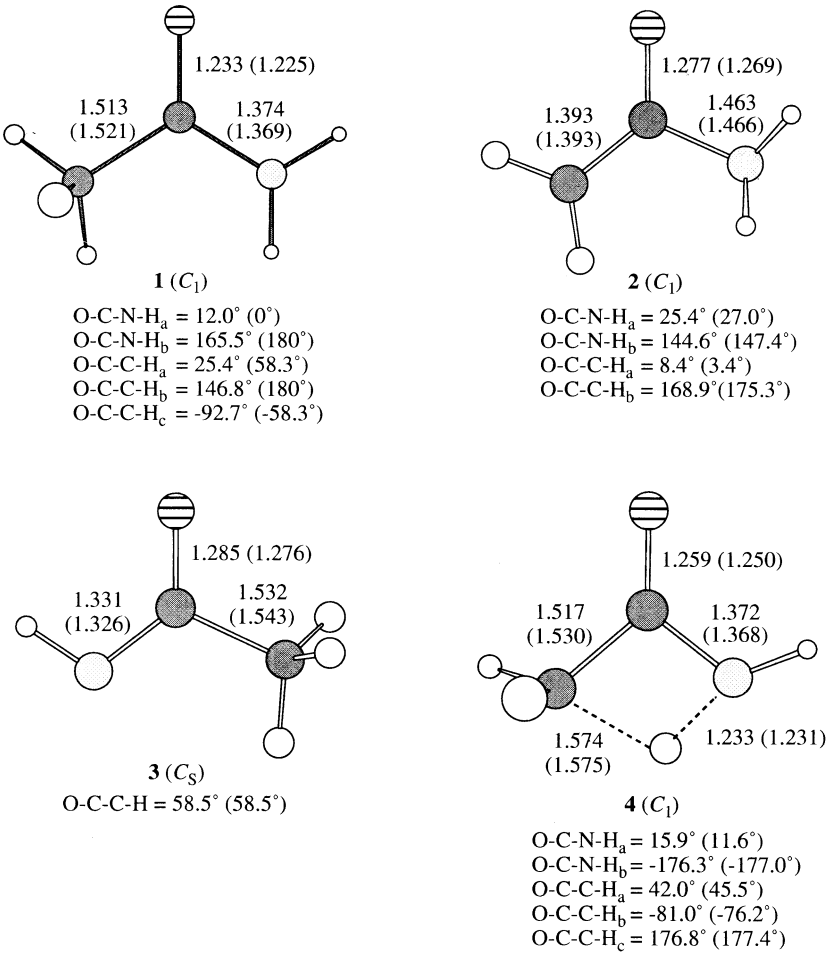


Fig. 1. Computed MP2 and B3LYP structures with the 6-31+G(*d*) basis set. Parenthetical values are for the B3LYP geometries.

[15] at −78 °C over a 15 min period. The product was obtained as a white solid (melting point 44 °C, 43–44 °C (lit.) [16]). *N*-(Trimethylsilyl)acetamide is commercially available but was synthesized by reacting acetamide with chlorotrimethylsilane and triethylamine in refluxing benzene.

Gas phase experiments were carried out with a dual cell model 2001 Finnigan FTMS equipped with a 3.0 T superconducting magnet. Fluoride ion was generated by electron ionization of carbon tetrafluoride at 6 eV and was allowed to react with 2-(trimethylsilyl)acetamide or *N*-(trimethylsilyl)acetamide to afford the ions of interest. The conjugate bases of acetamide were isolated by using a combination of chirp broadband excitations [17] and stored waveform inverse Fourier transform waveforms [18] and were vibrationally cooled with pulses of argon ($\geq 10^{-5}$ Torr). Their chemistry was then explored in one cell or the other as a function of time by allowing them to react with static pressures ($\sim 10^{-8} - 10^{-7}$ Torr) of selected probe reagents.

A variable temperature flowing afterglow-triple quadrupole device, which has previously been described, also was used for these experiments [19,20]. Fluoride ion was generated by electron ionization of nitrogen trifluoride. This ion and the helium buffer

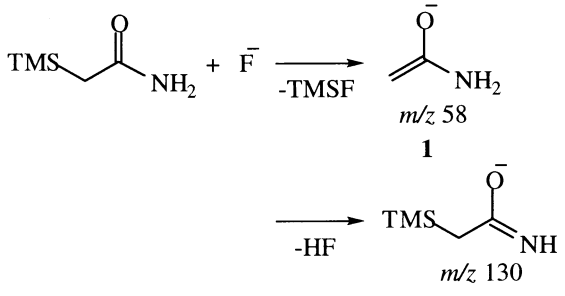
Table 1
Proton affinity bracketing results for acetamide enolate (**1**)[a]

Ref. cmpd.	ΔG°_{acid}	ΔH°_{acid}	Proton transfer
D_2O	386.1 ± 0.3	393.0 ± 0.2	No[b]
CH_3CH_2OD[c]	371.7 ± 1.1	378.3 ± 1.0	No[b]
t-BuOD[c]	368.0 ± 2.0	374.6 ± 2.1	No[d]
FCH_2CH_2OH	364.6 ± 2.8	371.2 ± 2.9	Yes (slow)
$CH_2{=}C(CN)CH_3$	364.1 ± 2.0	370.7 ± 2.1	Yes (slow)
$PhCH_2OH$	363.4 ± 2.0	370.0 ± 2.1	Yes (slow)
CH_3COCH_3	361.9 ± 2.0	369.1 ± 2.1	Yes
m-$CH_3C_6H_4NH_2$	359.6 ± 2.0	366.8 ± 2.1	Yes
CF_3CD_2OD[c]	354.1 ± 2.0	361.7 ± 2.5	Yes[e]

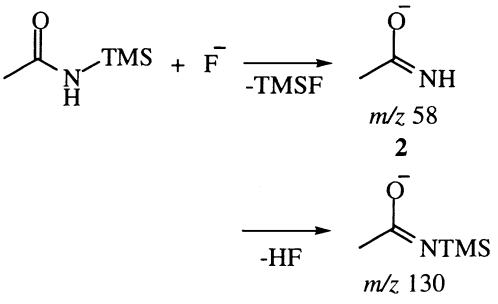
[a]Acidities come from [24]
[b] Incorporation of 1 D is observed.
[c] Acidity for the protio compound is given.
[d] Incorporation of two deuterium atoms is observed. The second one takes place slowly and only to a small extent.
[e] Incorporation of 1 D to a small extent is observed.

gas (P_{He} = 0.30 – 0.40 Torr) were allowed to flow 31–51 cm before coming into contact with one of the (trimethylsilyl)acetamides in order to establish laminar flow and temperature equilibration before the conjugate bases of acetamide were generated. Chemical reactions were explored by the addition of selected reagents at fixed points downstream and monitoring the ionic products with a triple quadrupole mass filter and standard pulse counting techniques. Collision-induced dissociation experiments were carried out using argon at chamber pressures ranging from 7×10^{-6} Torr to 2×10^{-5} Torr; the actual pressures in Q2 undoubtedly are greater. At the higher pressure the parent ion's intensity was reduced by approximately 80%. Since the flowing afterglow results are very similar to those obtained with the Fourier transform mass mspectrometry (FTMS), and to avoid any confusion, only the latter results are given unless specifically stated otherwise.

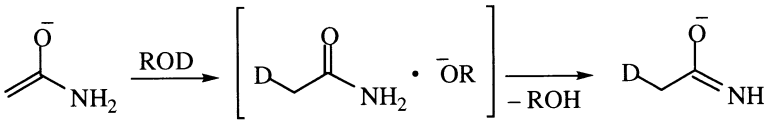
Ab initio and density functional theory calculations were carried out using GAUSSIAN 98 [21] and earlier versions of this program on SGI and IBM workstations. Full geometry optimizations of acetamide, its conjugate bases, and the transition structure interconverting the C- and N-deprotonated species were carried out at the Hartree-Fock (HF), second-order Møller-Plesset (MP2), and Becke 3-parameter- Lee-Yang-Parr (B3LYP) exchange-correlation functional (B3LYP) levels with the 6-31+G(*d*) basis set (Fig. 1). Analytical vibrational frequencies at each level of theory were computed to verify the nature of each stationary point (minima have positive force constants and transition structures have one imaginary frequency) and to obtain zero-point energies (ZPEs) and



Eq. 1.



Eq. 2.



Eq. 3.

thermal corrections from 0 to 298 K. Empirical scaling factors of 0.9135 (HF), 0.9646 (MP2), and 1.00 (B3LYP) were used for the ZPE and 0.8929 (HF), 0.9427 (MP2), and 1.00 (B3LYP) were used for the harmonic frequencies [22]. Single-point energy determinations were carried out at the B3LYP/6-31+G(*d*), QCISD(T)/6-311++G(*d*,*p*) and CCSD(T)/6-311+G(2*df*,2*pd*) levels of theory. In all cases, the proton affinities and rearrangement barriers have been ZPE and thermally corrected to 298 K.

3. Results and discussion

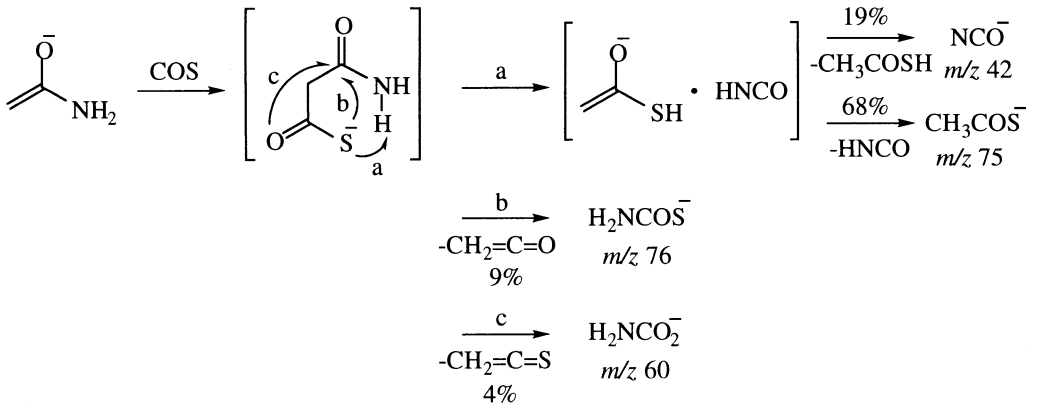
The acidity of acetamide at nitrogen [$\Delta H°_{acid}(CH_3CONH_2]$ = 362.0 ± 2.1 kcal mol^{-1}) has been measured by equilibrium techniques in a Fourier transform mass spectrometer by Taft and Gal [23,24]. This was accomplished because under thermodynamically controlled conditions it is reasonable to assume that only N-deprotonation takes place and that proton abstraction at carbon is energetically less favorable. Under kinetically controlled conditions C-deprotonation is expected to compete with N-deprotonation given that Grabowski and Cheng found that acetic acid enolate ($^-CH_2CO_2H$) is formed along with acetate ion ($CH_3CO_2^-$) upon reaction of acetic acid with strong bases [25]. To avoid this potential problem and minimize any isomeric contamination, we decided to generate acetamide enolate (**1**) and the authentic nitrogen anion isomer (**2**) via regioselective fluoride-induced desilylation reactions (Eqs. 1, 2). In both cases deprotonation (most likely at nitrogen) is competitive with the formation of the desilylated product.

The proton affinity of acetamide enolate **1** was determined by bracketing as shown in Table 1. Proton transfer was observed with acetone ($\Delta G°_{acid}$ = 361.9 ± 2.0 kcal mol^{-1}) and stronger acids but not with *tert*-butanol ($\Delta G°_{acid}$ = 368.0 ± 2.0 kcal mol^{-1}) and weaker acids. 2-Fluoroethanol, 2-cyanopropene, and benzyl alcohol ($\Delta G°_{acid}$ = 364.6 ± 2.8, 364.1 ± 2.0, and 363.4 ± 2.0 kcal mol^{-1}, respectively) react with **1** slowly while D_2O, EtOD, and *t*-BuOD lead to the incorporation of one deuterium atom into the ion by way of an acid-catalyzed isomerization to **2** (Eq. 3).

Table 2
Computed proton affinities, relative energies, and isomerization barriers[a]

Level[b]	PA		$\Delta H°_{rxn}$	$\Delta H°^{‡}$
	1	**2**	**(1–2)**	**(1→2)**
MP2/6-31+G(*d*)//HF	378.1	359.3	18.6	37.8
MP2/6-31+G(*d*)	378.2	359.4	18.8	38.4
QCISD(T)/6-311++G(*d*,*p*)	382.9	366.6	16.3	36.4
MP2/6-311+G(2*df*,2*pd*)//MP2	378.7	364.1	14.6	36.2
MP3/6-311+G(2*df*,2*pd*)//MP2	382.9	369.1	13.8	39.2
MP4(SDQ)/6-311+G(2*df*,2*pd*)//MP2	383.2	368.3	14.9	38.7
CCSD/6-311+G(2*df*,2*pd*)//MP2	383.3	368.5	14.8	38.9
CCSD(T)/6-311+G(2*df*,2*pd*)//MP2	381.4	366.5	14.9	36.9
B3LYP/6-31+G(*d*)	376.6	360.0	16.7	36.7
Experiment	373 ± 3	362.1 ± 2.1	11 ± 4	≥32

[a]All values are at 298 K, include ZPE corrections, and are in kcal mol^{-1}.
[b]HF and MP2 geometries are with the 6-31+G(*d*) basis set.



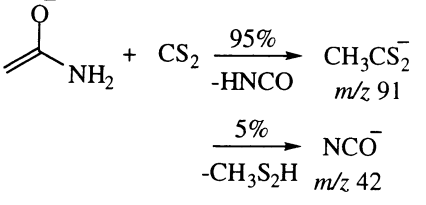
Eq. 4.

An additional deuterium is slowly incorporated into the amidate anion only in the case of *t*-BuOD as it is too weakly basic to react with the other deuterated acids; this was confirmed by independently reacting **2** with D_2O, EtOD, and *t*-BuOD. These results suggest $\Delta G°_{acid}(CH_3CONH_2)$ = 365 ± 3 kcal mol^{-1}, and when combined with a calculated entropy change for deprotonation (MP2/6-31+G(*d*) vibrational frequencies for acetamide and acetamide enolate were used) [26], a proton affinity for acetamide enolate [$\Delta H°_{acid}(CH_3CONH_2)$] of 373 ± 3 kcal mol^{-1} is obtained. This latter value is a little smaller than for *N*,*N*-dimethylacetamide ($\Delta H°_{acid}$ = 374.8 ± 3.6 kcal mol^{-1}) which is in accord with the previously reported acidity difference between acetic acid and methyl acetate ($\Delta H°_{acid}$ = 368.1 ± 3.1 and 371.8 ± 2.1 kcal mol^{-1}, respectively) [24,25].

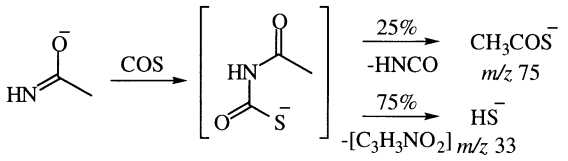
In strict terms our measured proton affinity is a lower limit because the reference acids used in the bracketing experiments can bring about the isomerization of **1** to **2**. A significantly larger value, however, would be inconsistent with the noted acidities of related compounds and previous observations that proton transfer is almost always observed when it is exothermic by at least a few kilocalories per mole [20,25,27]. Moreover, MP2 and B3LYP calculations (Table 2), two methods (particularly the latter) which are known to give accurate acidities [28,29], are in reasonable accord with experiment. Computationally more intensive CCSD(T)/6-311+G(2*df*,2*pd*) proton affinities, disappointingly, give poorer results for **1** and **2**, and are systematically too large by 8.4 and 4.4 kcal mol^{-1}, respectively. Regardless, the predicted deprotonation energies suggest that the true value probably is on the high side of our experimental range.

Acetamide enolate reacts with carbonyl sulfide to give several fragmentation products as shown in Equation 4. The major product is thioacetate (*m/z* 75, 68%) which presumably is accompanied by the loss of HNCO. Smaller amounts of NCO^- (*m/z* 42, 19%), H_2NCOS^- (*m/z* 76, 9%), and $H_2NCO_2^-$ (*m/z* 60, 4%) also are formed. The latter two species can be rationalized as arising from intramolecular attack within the initial adduct by sulfur or oxygen on the carbonyl group and subsequent, or simultaneous, loss of ketene or thioketene (paths b and c). In an analogous fashion, **1** reacts with carbon disulfide to give $CH_3CS_2^-$ and NCO^- in a 95:5 ratio (Eq. 5).

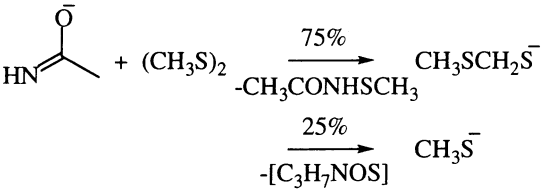
Amidate anion **2** is much less reactive with these reagents and can readily be distinguished from **1**. No reaction is observed with CS_2 whereas COS slowly



Eq. 5.



Eq. 6.



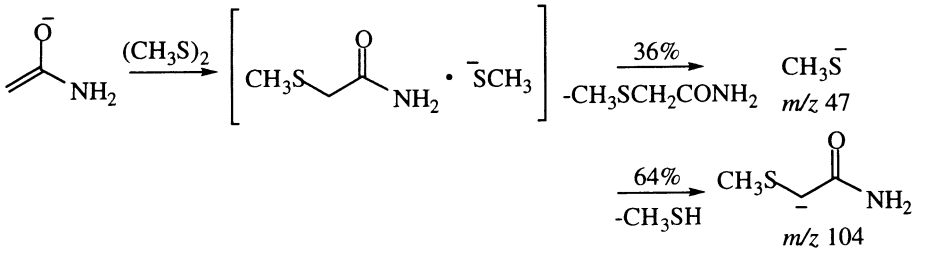
Eq. 8.

reacts with **2** to afford HS^- and thioacetate in a 3:1 ratio (Eq. 6).

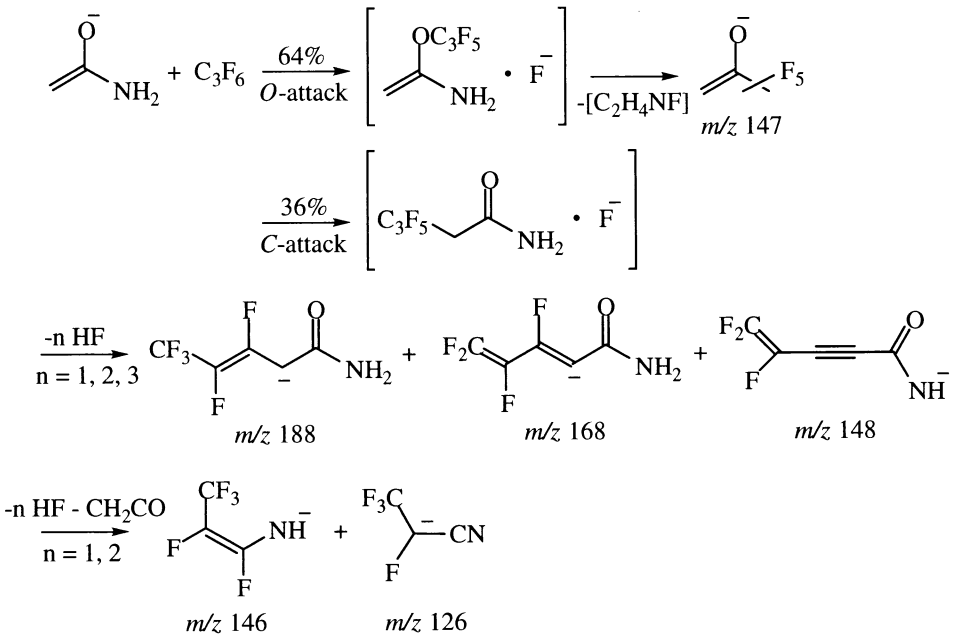
Dimethyl disulfide is a useful reagent for distinguishing between anionic isomers [30]. Enolates typically give rise to methanethiolate and thiomethylated products, and **1** is no exception. It affords CH_3S^- (*m/z* 47, 36%) and α-thiomethylacetamide enolate (*m/z* 104, 64%) (Eq. 7). In contrast, N-deprotonated acetamide gives the elimination product $CH_3SCH_2S^-$ (*m/z* 93) and CH_3S^- in a 3:1 ratio along with a minor amount of HS^- (Eq. 8).

Like other enolate ions, acetamide enolate is an ambident nucleophile that can react with electrophiles either through its oxygen or carbon centers. Reagents such as perfluoropropylene and perfluorobenzene have been developed to give a quantitative measure of reaction resulting from the two nucleophilic sites [31–41]. In the former case the O-/C-attack ratio is 64:36 (Eq. 9) whereas in the latter instance it is 6:94 (Eq. 10). This contrasts with the 1:99 (ion cyclotron resonance (ICR)) [40] and 5:95 [flowing afterglow (FA)] [32] O/C ratios previously reported for the reaction of *N,N*-dimethylacetamide enolate with perfluoropropylene, but is similar to the 1:99 O/C ratio observed with perfluorobenzene [40]. Our results also are in accord with the general finding that perfluorobenzene gives smaller O/C ratios than perfluoropropylene. For comparison sake, we also examined the reactions of *N*-deprotonated acetamide with perfluoropropylene and perfluorobenzene even though they previously have been described. Our results are in excellent accord with those of Freriks, de Koning, and Nibbering [41] (Table 3).

Collision activated dissociation of **1** at low (1–5 eV, lab) kinetic energies using sustained off-resonance irradiation (SORI) [42] and argon as the collision gas results in two fragment ions, NCO^- (*m/z* 42) and $HC{\equiv}CNH^-$ (*m/z* 40) ($^-CH_2CN$ is a possible alternative structure, but its formation seems less likely mechanistically). The NCO^-:$HC{\equiv}CNH^-$ ratio is very sensitive to the nominal kinetic energy of the ions and varies from 1.6 to 67 as the energy is increased (Table 4). Formation of the latter ion can be explained by loss of water in two steps as shown in Eq. 11. Isocyanate, on the other hand, presumably arises by means of isomerization of **1** to **2** followed by methyl anion expulsion and rapid proton transfer. Direct on-resonance collision-induced dissociation of **1** leads to three additional fragment ions at higher energies [NH_2^- (*m/z* 16), HO^- (*m/z* 17), and $HC{\equiv}CO^-$ (*m/z* 41)]. Both the amide and hydroxide ions arise from simple bond cleavages while the conjugate base of ketene results from the loss of ammonia in a two



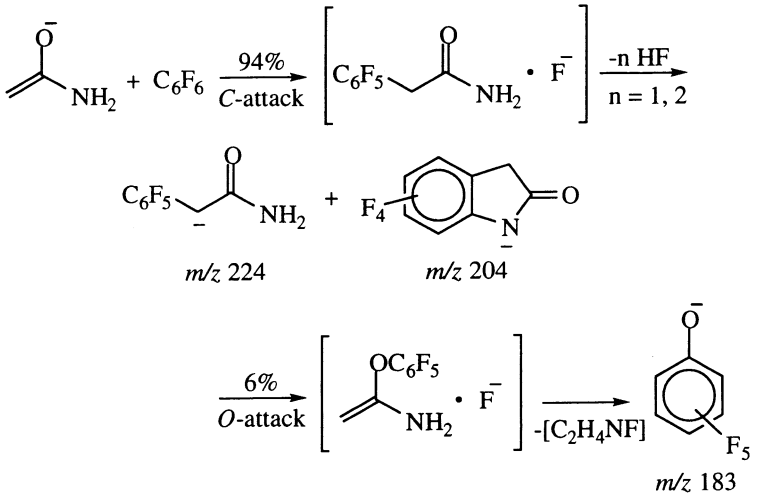
Eq. 7.



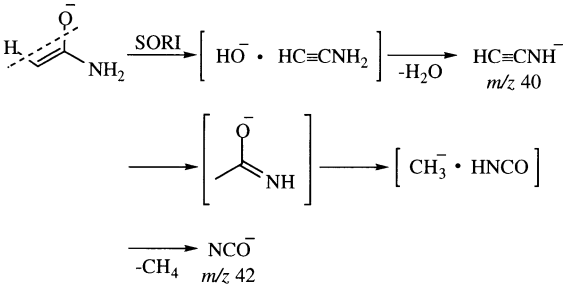
Eq. 9.

step process; amide ion loss followed by proton abstraction. In comparison, both SORI and on-resonance CID of **2** give NCO^- as the only fragment ion. These results are consistent with the fragmentation "rules" developed by Bowie and co-workers [43–46] and the observation that acetic acid enolate isomerizes to acetate upon collisional activation [47], but contrasts with the conversion of acetate anion back to acetic acid enolate under higher energy conditions.

Acetamide enolate and its amidate anion also were generated in a variable temperature FA device. Their reactivity is similar to that observed in our FTMS and



Eq. 10.



Eq. 11.

the differences can be accounted for by the approximately 10^7 difference in operating pressures. For example, adduct anions are observed in the FA reactions of **1** with COS and CS_2 because rapid cooling by third-body collisions can remove much of the excess internal energy whereas in the lower pressure regime of the FTMS this reaction channel is inefficient and only fragmentation products are produced. A more detailed comparison of the FA and FTMS data is given in Table 5.

Unimolecular rearrangements can be probed with a variable temperature flowing afterglow apparatus [48,49]. Isomerization of acetamide enolate to its amidate anion is exothermic by 11 ± 4 kcal mol^{-1} [−14.9 and −16.7 kcal mol^{-1} at the CCSD(T)/6-311+G(2*df*,2*pd*)//MP2/6-31+G(*d*) and B3LYP/6-31+G(*d*) levels, respectively] and could take place via a 1,3 proton shift, but there is no evidence for the occurrence of this process in either our FA or FTMS. In order to probe the barrier for the **1** to **2** isomerization, we heated both ions to 100, 200, and 300 °C and examined their reactivity with perfluoropropylene and CID spectra. No changes were observed over this temperature range which indicates that **1** does not convert to **2** under these conditions. If we assume an Arrhenius A factor of 10^{13} for this isomerization, then given the sensitivity and flow characteristics of our

Table 3
Comparisons of the product ratios of **1**, *N*,*N*-dimethylacetamide enolate, and **2** with perfluoropropylene and perfluorobenzene

		Product ratio		
Ion	Reagent	%C	%O	%N
1	C_3F_6	36	64	
	C_6F_6	94	6	
$^-CH_2CON(CH_3)_2$[a]	C_3F_6	99(95)	1(5)	
	C_6F_6	99	1	
2[b]	C_3F_6		39(34)	61(66)
	C_6F_6		0(1)	100(99)

[a]ICR results [40] are given first, FA data (in parentheses) [32] follow.
[b]Our results are given first, ICR data (in parentheses) [40] follow.

Table 4
Kinetic energy dependence of the collision-induced dissociation of acetamide enolate

		Product ratio[a]				
Process	KE (eV, lab)	NH_2^- (*m/z* 16)	HO^- (*m/z* 17)	$HC{\equiv}CNH^-$ (*m/z* 40)	$HC{\equiv}CO^-$ (*m/z* 41)	NCO^- (*m/z* 42)
SORI[b]	1.14			38%		62%
	1.79			9%		91%
	3.19			1%		99%
CID	7.3			12%	12%	76%
	11.5			8%	18%	75%
	18.3	3%	3%	9%	29%	56%

[a]Each row has been normalized to sum up to 100 ± 1%.
[b]Nominal kinetic energies of the ions, multiple collisions give higher internal energies.

Table 5
Comparison of enolate and amidate reactivity in a Fourier transform mass spectrometer and a flowing afterglow device

	FTMS		FA	
Reagent	**1**	**2**	**1**	**2**
COS	NCO^- (*m/z* 42, 19%) $NH_2CO_2^-$ (*m/z* 60, 4%) CH_3COS^- (*m/z* 75, 68%) NH_2COS^- (*m/z* 76, 9%)	HS^- (*m/z* 33, 70%) CH_3COS^- (30%)	NCO^- (20%) CH_3COS^- (25%) Adduct (*m/z* 118, 55%)	CH_3COS^- (trace) Adduct
CS_2	NCO^- (*m/z* 42, 4%) $CH_3CS_2^-$ (*m/z* 91, 96%)	No rxn	NCO^- (10%) $CH_3CS_2^-$ (80%) Adduct (*m/z* 134, 10%)	No rxn
$(CH_3S)_2$	CH_3S^- (*m/z* 47, 36%) $CH_3SCH^-CONH_2$ (*m/z* 104, 64%)	HS^- (*m/z* 33, 5%) CH_3S^- (24%) $CH_3SCH_2S^-$ (*m/z* 91, 71%	CH_3S^- (~58%) $CH_3SCH^-CONH_2$ (~42%)	No rxn
C_3F_6	*O*-attack (*m/z* 147, 64%) *C*-attack (*m/z* 188, 168, 148, and 126, 36%)	*O*-attack (*m/z* 147, 39%) *N*-attack (*m/z* 188, 168, 146, and 126, 61%)	*O*-attack (*m/z* 147, ~75%) *C*-attack (*m/z* 188, and 148, ~25%)	*O*-attack (*m/z* 147, ~20%) *N*-attack (*m/z* 188, 80%)
C_6F_6	*O*-attack (*m/z* 183, 6%) *C*-attack (*m/z* 204 and 224, 94%	*N*-attack (*m/z* 204 and 182, 100%	*O*-attack (*m/z* 183, ~50%) *C*-attack (*m/z* 224, ~50%)	*N*-attack (*m/z* 224, 100%)
CID[a]	NH_2^- (*m/z* 16) HO^- (*m/z* 17) $HC{\equiv}CNH^-$ (*m/z* 40) $HC{\equiv}CO^-$ (*m/z* 41) NCO^- (*m/z* 42)	NCO^- (100%)	NH_2^- (trace) $HC{\equiv}CO^-$ (~25%) NCO^- (~75%)	NCO^- (100%)

[a]See text for additional details.

flowing afterglow device [49], an activation energy of at least 32 kcal mol^{-1} can be derived for the rearrangement of **1** to **2**. In accord with this result, ab initio and density functional theory calculations using a variety of methods and basis sets all predict a barrier of around 37 kcal mol^{-1}. Examination of the transition structure (Fig. 1) reveals that the C–C and C–N bond lengths are almost identical to those of acetamide indicating that the C=C double bond character in **1** is lost and is not recovered in the C–N bond. The methylene group is rotated out of the plane formed by the heavy atoms which leads to the conclusion that the barrier height is almost entirely due to the rotation of the C–C bond in acetamide enolate because an essentially unstabilized carbanion results.

4. Conclusions

Acetamide enolate (**1**) can readily be prepared by the fluoride-induced desilylation of 2-(trimethylsilyl)acetamide. It is stable with respect to a 1,3 proton shift and isomerization to amidate anion **2** to a temperature of 300 ° or higher. This indicates that the rearrangement barrier is at least 32 kcal mol^{-1}, which is in good accord with ab initio and DFT computed values ranging from 36.2 to 39.2 kcal mol^{-1}. The proton affinity of **1** was measured by bracketing experiments and is 373 ± 3 kcal mol^{-1} which means that the carbon anion is 11 ± 4 kcal mol^{-1} more basic than the isomeric nitrogen anion. Both of these values are in reasonable agreement with MP2/6-31+G(*d*) and B3LYP/6-31+G(*d*) predictions, but computationally more intensive CCSD(T)/6-311+G(2*df*,2*pd*) energies only reproduce the acidity difference (14.9 kcal mol^{-1}); the absolute values are systematically too large. Reactivity studies with a variety of probe reagents also were carried out, and the ambident nature of **1** was explored with perfluoropropylene and perfluorobenzene. In the former case, acetamide enolate reacts predominately (64%) by way of O-attack

whereas with the latter reagent C-attack dominates (94%). These results are consistent with the behavior of other ambident nucleophiles as elucidated by Nibbering and his research group over the course of many productive years.

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