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A Prototype for Catalyzed Amide Bond Cleavage: Production of the $[NH_3, H_2O]^{\bullet+}$ Dimer from Ionized Formamide and Its Carbene Isomer

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Abstract: The reaction of ionized formamide $H_2NCHO^{\bullet+}$ with water leads to an exclusive loss of CO from the complex. This contrasts with the unimolecular reaction of low-energy ionized formamide, which loses exclusively one hydrogen atom. The unimolecular loss of CO is not observed because it involves several H-transfers corresponding to high-energy barriers. Experimental and theoretical studies of the role of solvation by water on the fragmentation of ionized formamide leads to three different results: (i) In contrast with different systems previously studied, in which solvation plays only a role on one or two steps of a reaction, a molecule of water is efficient in the catalysis of the decarbonylation process because water catalyzes all the steps of the reaction of ionized formamide, including the final dissociation of the amide bond. (ii) The catalyzed isomerization of carbonylic radical cations into their carbene counterparts is shown to be an important step in the process. To study this step, a precise probe, characterizing the carbene structure by ion−molecule reaction, is for the first time described. (iii) Finally, decarbonylation of ionized formamide yields the $[NH_3, H_2O]^{\bullet+}$ ion, which has not been generated and experimentally studied previously. By this method, the $[NH_3, H_2O]^{\bullet+}$ ion is generated in abundance and with a low internal energy content, allowing one either to prepare, by ligand exchange, a series of other solvated radical cations or to generate covalent structures such as distonic ions. First results on related systems indicate that the conclusions obtained for ionized formamide are widespread.

Introduction

During the past decade, a great number of works deals with the influence of solvent on the pathway of reaction in the gas phase. These works concern small ions[1−6] as well as larger ones such as peptides, in order for instance to study water-assisted proton mobility.[7]

Depending on the system under study, a neutral molecule can have opposite influences on the decomposition of an ion. From scattered results in the literature, it is proposed herein to distinguish between three main effects. A first effect always operates on the initial state. The solvation of an ion by a neutral molecule creates a complex [ion, solvent] or a covalent structure, both of which can be strongly stabilized and can therefore possess a great excess of internal energy, allowing it to pass a number of energy barriers.[1−6]

A second effect can take place on the transition states. A neutral molecule can catalyze proton transports, leading to the isomerization of the initial molecular ion. To be efficient in such a process, the solvent molecule must interact directly with the transferred hydrogen in the transition state. For instance, it has been shown both by experiment and by calculation[2] that one molecule of water catalyzes the 1,2-H shift that converts ionized methanol $CH_3OH^{\bullet+}$ into its more stable isomer, the

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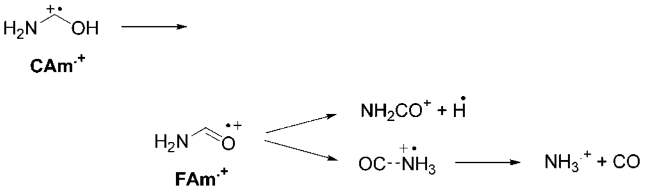
Scheme 1



α-distonic ion ${}^{\bullet}CH_2OH_2^+$ (eq 1). The mechanism of this reaction has been clearly established while a significant number of other 1,2-H^+ transports have been described.[3]

$$CH_3OH^{\bullet+}, H_2O \rightarrow [H_2O^+H\cdots{}^{\bullet}CH_2OH] \rightarrow [{}^{\bullet}CH_2O^+(H)H\cdots OH_2] \rightarrow {}^{\bullet}CH_2OH_2^+, H_2O \quad (1)$$

1,3-H^+ transfers from heteroatom to heteroatom,[4] which also involve high-energy barriers, can be catalyzed by a solvent molecule, while several catalyzed keto−enol tautomerism reactions have been studied in cations[5] as well as in radical cations.[6] In all the studied examples, catalysis facilitates some of the pathways connecting the intermediates in the unimolecular fragmentation by lowering the energy barriers. In some cases, the mechanism of the catalyzed reaction can be different from that of the unimolecular reaction of the bare ion.[6f] Finally, when the solvent molecule is only a spectator in a H-transfer, the activation energy is generally the same, if not greater, for the solvated ion as for the bare ion.

A third effect of solvation can be a strong stabilization of the final state. For instance, it is well-known[8] that an extensive H-exchange occurs prior to the dissociation of protonated ethanol, since the transition state, connecting protonated ethanol and the $[H_3O^+, C_2H_4]$ complex, lies below the final states energy (eq 2).

$$C_2H_5OH_2^+ \rightleftarrows [H_3O^+, C_2H_4] \rightarrow H_3O^+ + C_2H_4 \quad (2)$$

In contrast, protonated ethanol solvated by a molecule of water fragments without H-exchange.[8] In this case, the initial and final states are proton-bound dimers and therefore strongly stabilized (by more than 20 kcal mol^{-1}). Conversely, the stabilization of the transition state is poor, since the water molecule is not in direct interaction with the transferred hydrogen (eq 3).

$$[C_2H_5OH_2^+, H_2O] \rightarrow [C_2H_4, H_3O^+, H_2O] \rightarrow [H_3O^+, H_2O] + C_2H_4 \quad (3)$$

As a consequence, solvation of protonated ethanol makes its reaction more difficult, compared to that of the bare ion, and irreversible.[8]

The potential energy surface for ionized formamide and other $[CNOH_3]^{\bullet+}$ ions with OCN connectivity involves several H-transfers steps corresponding to high-energy barriers (Scheme 1 and Figure 1).[9] This surface explains why ionized formamide loses $H^{\bullet}$ in the metastable ion energy frame, whereas its carbene isomer ($HO-C-NH_2^{\bullet+}$) loses either $H^{\bullet}$ or CO under similar conditions. This work reports the role of solvation by water on the fragmentation and isomerization of ionized formamide. Formation of the $[NH_3, H_2O]^{\bullet+}$ dimer, generated for the first time, is the main reaction product. The bimolecular reactivity of this ion, allowing either the preparation of other solvated radical cations or the generation of covalently bound structures, such as distonic ions, is also reported.

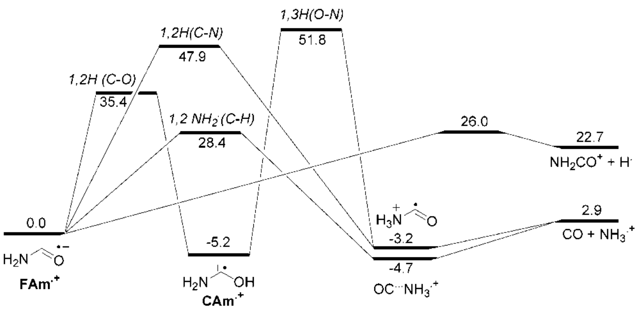


Figure 1. Potential energy surface of the unimolecular decomposition of ionized formamide (**FAm**$^{\bullet+}$) and its carbene isomer (**CAm**$^{\bullet+}$) calculated at the G2(MP2,SVP) level of the theory (kcal mol^{-1}). Values from ref 9c.

Experimental and Computational Procedures

Ion−Molecule Reactions. The bimolecular reactions of ions were examined in a Bruker CMS-47X FT-ICR mass spectrometer[10] equipped with an external ion source[11] and an infinity cell.[12] Reagents were all commercially available and used without further purification. Liquid reagents introduced through the leak valve assembly were thoroughly degassed through several freeze−pump−thaw cycles. The neutral reactants were introduced into the cell through a leak valve at a pressure from 1×10^{-8} to 4×10^{-8} mbar (depending on the experiment) and then diluted with argon to give a total pressure of 2×10^{-7} mbar. Where appropriate, neutral reactant was introduced by means of a solenoid pulsed valve.

Ion−molecule reactions were examined after isolation and thermalization of the reactant ions formed in the external ion source. After transfer into the cell, the ion of interest was first isolated by on-resonance radio frequency (rf) ejection of all unwanted ions. After a 1.5 s delay (usually sufficient to thermalize the ions by successive collisions with argon), the isolation procedure was repeated by the use of low-voltage single rf pulses (soft shots) at the resonance frequencies of the product ions formed during the relaxation time. Low energy collision induced dissociations (CID) of ions were performed by exciting kinetically the ion of interest with an on-resonance rf pulse (peak to peak voltage $V_{p-p} = 18$ V, pulse duration 40−160 μs) and allowing the ions to collide with argon (2×10^{-7} mbar) for 50−100 ms.

The efficiencies of the reactions are reported as the ratio of the experimental rate constant to the calculated collision rate constant according to the method of Su and Chesnavich.[13]

Formation of the Reactant Ions. Ionized formamide ($NH_2CHO^{\bullet+}$, **FAm**$^{\bullet+}$), ionized formic acid ($HCOOH^{\bullet+}$) and acetaldehyde ($H_3CCHO^{\bullet+}$) radical cations, labeled or unlabeled, were generated by ionization of the corresponding compounds. Their carbene counterparts were generated[14] by fragmentation of ionized oxamide for $HO-C-NH_2^{\bullet+}$ (**CAm**$^{\bullet+}$), of ionized oxalic acid for $HO-C-OH^{\bullet+}$, and of ionized pyruvic acid for $H_3C-C-OH^{\bullet+}$. $HOCH{=}NH^{\bullet+}$ was obtained by fragmentation of ionized *N,N′*-diformylhydrazine.[15]

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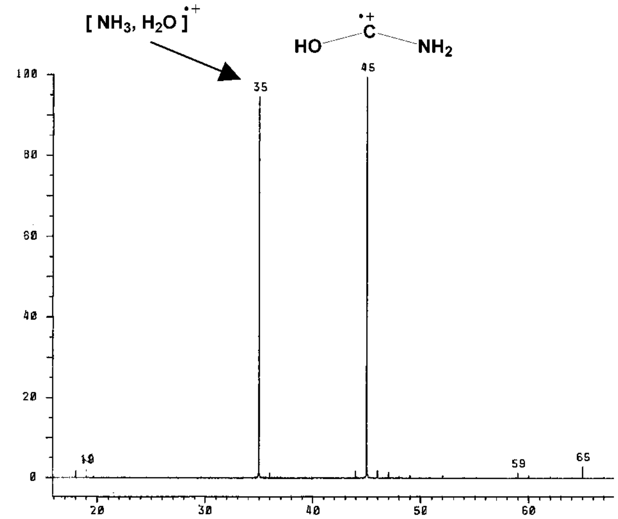


Figure 2. Spectrum of ionized formamide **FAm**$^{•+}$ after 5 s of reaction with water (1.5×10^{-8} mbar).

Calculations. The Gaussian 98[16] program package was used for calculations to determine the different key structures on the potential energy profile. The G3(MP2)//B3LYP[17] method was used to optimize the geometry and determine the energies: the geometries were optimized at the B3LYP/6-31G* level of the theory. Since numerous structures are noncovalent structures involving hydrogen bonds, a method taking into account electronic correlation is necessary for accurate geometries. The B3LYP method includes parametrization of electron correlation and is less expensive in computing time than ab initio methods (MP2 or CI). The geometries at the B3LYP/6-31G* level were also compared to those obtained at the UMP2/6-31G* level of the theory and differed markedly only for some transition states (see the discussion).

Diagonalization of the computed Hessian was performed at the B3LYP/6-31G* level of the theory in order to confirm that the structures were minima or transition states on the potential energy surface. Vibration frequencies, computed at this level of theory and scaled by an empirical 0.96 factor,[17] led to the calculation of zero-point energy corrections and of thermal energy and enthalpy corrections at 298.15 K.

Results and Discussion

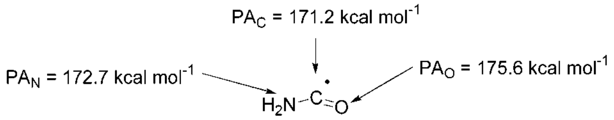
In the presence of water, $NH_2CHO^{•+}$ (**FAm**$^{•+}$) and its carbene isomer $NH_2{-}C{-}OH^{•+}$ (**CAm**$^{•+}$) yield only one product, $NOH_5^{•+}$ (*m*/*z* 35, Figure 2), by loss of CO. In both cases, the collision-induced dissociation of this ion leads exclusively to ionized ammonia, $NH_3^{•+}$ (*m*/*z* 17). The structure of this ion will be shown to be the ionized ammonia−water dimer [$NH_3^{•+}$, H_2O]. The same reactions performed with labeled water ($H_2{}^{18}O$) show exclusive formation of the [$NH_3^{•+}$, $H_2{}^{18}O$] dimer. Therefore, the oxygen atom in the CO moiety comes from the **FAm**$^{•+}$ or **CAm**$^{•+}$ ions.

Table 1. Calculated (G3(MP2)//B3LYP) Energies and Enthalpies of the Various $CNOH_3^{•+}$ Isomer Ions and of the $NH_2CO^{•}$ Radical

	$\Delta E°$ [a]	$\Delta H°$ [b]
$NH_2CHO^{•+}$	0.0	0.0
$NH_2COH^{•+}$	4.7	4.4
$NH_3CO^{•+}$	2.0	1.5
$NH_2CO^{•} + H^+$	171.8	171.2

[a] Energies in kcal mol^{-1}, relative to ionized formamide. [b] Enthalpies in kcal mol^{-1}, relative to ionized formamide.

Scheme 2. Calculated Proton Affinities of the NH_2CO• Radical



1. Catalyzed Isomerization of Ionized Formamide. The experimental efficiency of formation (k/k_{coll}) of the [$NH_3^{•+}$, H_2O] dimer from **FAm**$^{•+}$ (0.05 ± 0.02) is nearly identical to that from **CAm**$^{•+}$ (0.05 ± 0.02). A fast catalyzed isomerization of ionized formamide into its more stable carbene counterpart (Table 1)[14] could explain these results.

To prove the existence of such a catalyzed isomerization, it is necessary to be able to characterize the carbene structure. The production and characterization of ionized carbenes, such as $XCY^{•+}$ (X, Y = H, CH_3, OH, NH_2...), have been studied in some detail in the past decade. Their structures and energetics have been studied by CID experiments of metastable ions and have been computationally investigated.[14] Contrastingly, they have not been characterized by ion−molecule reactions, despite their very unique structure presenting an empty orbital and a singly occupied orbital on a carbon atom, which is a potential electrophilic or radical-type reactive center.

Since collision-induced dissociations of **FAm**$^{•+}$ and **CAm**$^{•+}$ do not allow a clear distinction between these structures under FT-ICR conditions, a characteristic reagent of **CAm**$^{•+}$ has been searched for, to determine whether water catalyses the isomerization of **FAm**$^{•+}$ into **CAm**$^{•+}$ or not, prior to *m*/*z* 35 formation.

The first difficulty in finding such a reagent is that it must not be efficient in the conversion of **FAm**$^{•+}$ into **CAm**$^{•+}$. The second difficulty is that **FAm**$^{•+}$ and **CAm**$^{•+}$ are rather strong acids. The proton affinities (PA) of the NH_2CO radical were calculated (values from Table 1) to be 175.6 kcal mol^{-1} at oxygen, 171.2 kcal mol^{-1} at carbon, and 172.7 kcal mol^{-1} at nitrogen (Scheme 2). Therefore, the main reaction of **FAm**$^{•+}$ and **CAm**$^{•+}$ (*m*/*z* 45) with a molecule is more often proton transfer to the neutral. It is the case with cyclopropane (PA = 179.3 kcal mol^{-1}).[18] However, in the reaction of **CAm**$^{•+}$ with cyclopropane, a characteristic minor channel (30%) is also open, leading to a $C_2H_5NO^{•+}$ (*m*/*z* 59) product ion whose reactivity toward different neutral molecules is identical to that of the enol counterpart of acetamide[6g] (Figure 3).

The mechanism of this reaction, which will be detailed elsewhere,[19] is probably an electrophilic and/or open shell attack of the carbene center on cyclopropane, resulting in a C−C bond formation with ring opening (Scheme 3). In the case of $NH_2COH^{•+}$, such a process leads to the intermediate distonic ion $NH_2{}^+C(OH)CH_2CH_2CH_2{}^{•}$, which eliminates ethylene by simple cleavage to yield the enol counterpart of acetamide,

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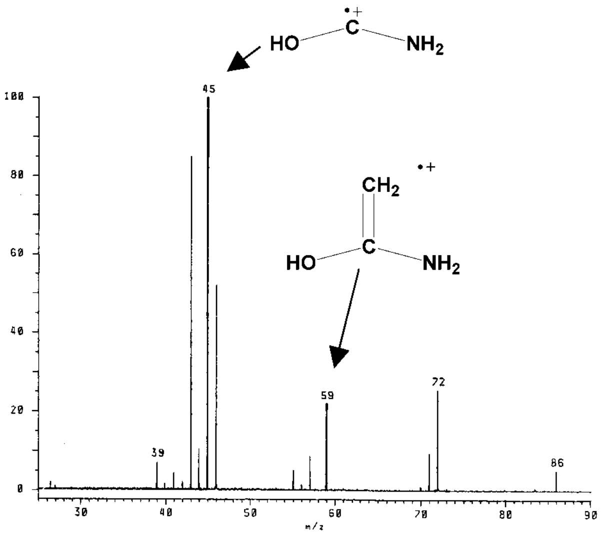
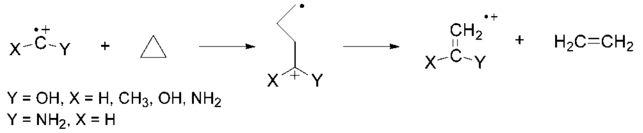


Figure 3. Spectrum of the reaction of ionized hydroxylamino carbene **CAm**$^{\bullet+}$ with pulsed cyclopropane.

Scheme 3. Reaction of Various Ionized Carbenes with Cyclopropane



NH$_2$CO(H)CH$_2^{\bullet+}$ (*m*/*z* 59). This characteristic reaction, not observed with the molecular ions, is widespread and operates with other carbene radical cations[19] such as HC−OH$^{\bullet+}$, HO−C−OH$^{\bullet+}$, HC−NH$_2^{\bullet+}$, or H$_3$C−C−OH$^{\bullet+}$.

Thus cyclopropane can be used as a probe to characterize **CAm**$^{\bullet+}$, and the following reactions were performed in order to prove experimentally its formation in a catalyzed isomerization. In a first one, **FAm**$^{\bullet+}$ is allowed to react with cyclopropane pulsed into the cell. No *m*/*z* 59 product is observed. In a second one, **FAm**$^{\bullet+}$ collides with water during 5 s ($p = 2 \times 10^{-8}$ mbar) prior to reisolation of the remaining *m*/*z* 45 ions. A pulse of cyclopropane is followed by the appearance of an *m*/*z* 59 product ion, which proves the conversion by water of **FAm**$^{\bullet+}$ into **Cam**$^{\bullet+}$ to be effective.

The potential energy surface for the catalyzed isomerization has been examined by ab initio calculations. As observed for ionized methanol[2] or ionized acetaldehyde,[6f] solvation of **FAm**$^{\bullet+}$ yields two stable [NH$_2$CHO$^{\bullet+}$, OH$_2$] complexes, **1** and **2** (Table 2, Figures 4 and 5). In the first one, the hydrogen of the CHO group interacts with the oxygen of water. In the second one, one amino hydrogen is involved in the H-bond with water.

Via the three-member transition state **1/3a**$_{(3\ \mathrm{center})}$ or the five-member one **1/3a**$_{(5\ \mathrm{center})}$ (Figures 4 and 5), **1** can convert into the more stable complex **3a**, [NH$_2$COH$^{\bullet+}$, OH$_2$], through a low-energy barrier. In ion **3a**, which can also be obtained by direct reaction of **CAm**$^{\bullet+}$ with water, the hydroxylic hydrogen is strongly bonded to the water oxygen. Since both **1/3a**$_{(3\ \mathrm{center})}$ and **1/3a**$_{(5\ \mathrm{center})}$ lie in energy only some kcal mol^{-1} above **1**, it can be proposed that the interconversion between **1** and **3a** is facile and, therefore, that water catalyzes the 1,2-H$^+$ transfer leading from **FAm**$^{\bullet+}$ to **CAm**$^{\bullet+}$. In contrast, it may be noted that, in the corresponding 1,2-H transfer leading from **2** to **4**, the water molecule can only act as a spectator; the transition state **2/4** is in consequence very high in energy.

Table 2. Energies of the Stable States, Reaction Product and Transition States for the Isomerization and Decarbonylation of **FAm**$^{\bullet+}$ + H$_2$O and **CAm**$^{\bullet+}$ + H$_2$O

	$\Delta E^{\circ\,a}$	
	B3LYP/6-31G*	G3(MP2)//B3LYP/6-31G*
NH$_2$CHO$^{\bullet+}$ + H$_2$O	0.0	0.0
[NH$_3^{\bullet+}$, H$_2$O] + CO	−12.0	−17.9
NH$_4^+$ + HOCO$^\bullet$	−27.1	−24.9
H$_3$O$^+$ + NH$_2$CO$^\bullet$	9.9	8.5
1	−24.6	−15.0
2	−23.0	−17.6
3a	−33.3	−30.1
3b	−28.2	−24.8
4	−22.1	−21.5
5	−22.3	−21.7
6	−19.8	−23.6
7	−46.8	−41.7
1/3a$_{(3\ \mathrm{center})}$	−16.6	−15.2
1/3a$_{(5\ \mathrm{center})}$	−17.0	−14.2
1/5$_{(3\ \mathrm{center})}$	−4.5	−3.0
1/5$_{(5\ \mathrm{center})}$	−4.2	−1.9
1/6	13.1	10.0
2/2	7.9	13.8
2/4	17.7	18.8
3a/3b	−18.4	−16.5
3a/7	12.6	17.5
3b/5	−11.1	−8.8
4/4	7.4	7.8

[a] Energies in kcal mol^{-1} are relative to **FAm**$^{\bullet+}$ + H$_2$O.

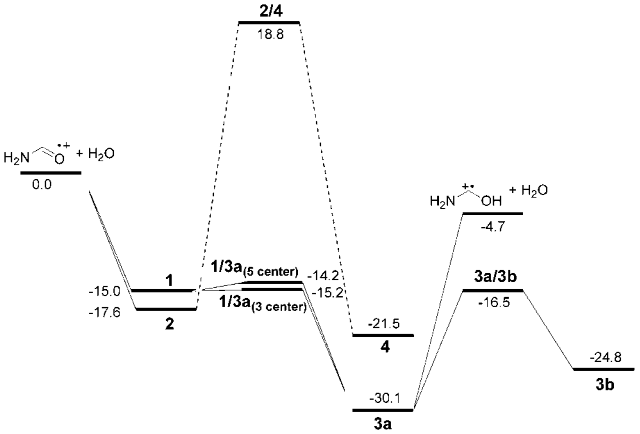


Figure 4. Potential energy surface of the water-catalyzed isomerization of ionized formamide (**FAm**$^{\bullet+}$) into its more stable carbene isomer (**CAm**$^{\bullet+}$) calculated at the G3(MP2)//B3LYP level of the theory (in kcal mol^{-1}). In dashed lines is a pathway prohibited for the reaction due to a transition state higher in energy than the reactants. The corresponding structures are reported in Figure 5.

H/D exchange experiments were performed in order to check that interconversion takes place between **1** and **3a**. In the presence of D$_2$O, **FAm**$^{\bullet+}$ and **CAm**$^{\bullet+}$ (*m*/*z* 45) exchange only one hydrogen, giving an *m*/*z* 46 ion, even for long reaction times. When the initial reactant is **FAm**$^{\bullet+}$, this exchanged ion has the carbene structure, according to its reaction with cyclopropane (production of C$_2$H$_4$DNO$^{\bullet+}$, *m*/*z* 60). This indicates that the hydrogens of the amino group are never involved in the process and that the *m*/*z* 46 ion is H$_2$N−C−OD$^{\bullet+}$. The exchange is a consequence of the $\mathbf{1} \rightleftarrows \mathbf{3}$ interconversion that can be followed by an easy interchange between **3a** and **3b** (Figure 4). When the initial reactant ion is **Cam**$^{\bullet+}$, the latter process is most probably operative. Examination of the potential energy surface also reveals why no exchange of the hydrogens of the amino group is observed. This exchange could occur in either one of

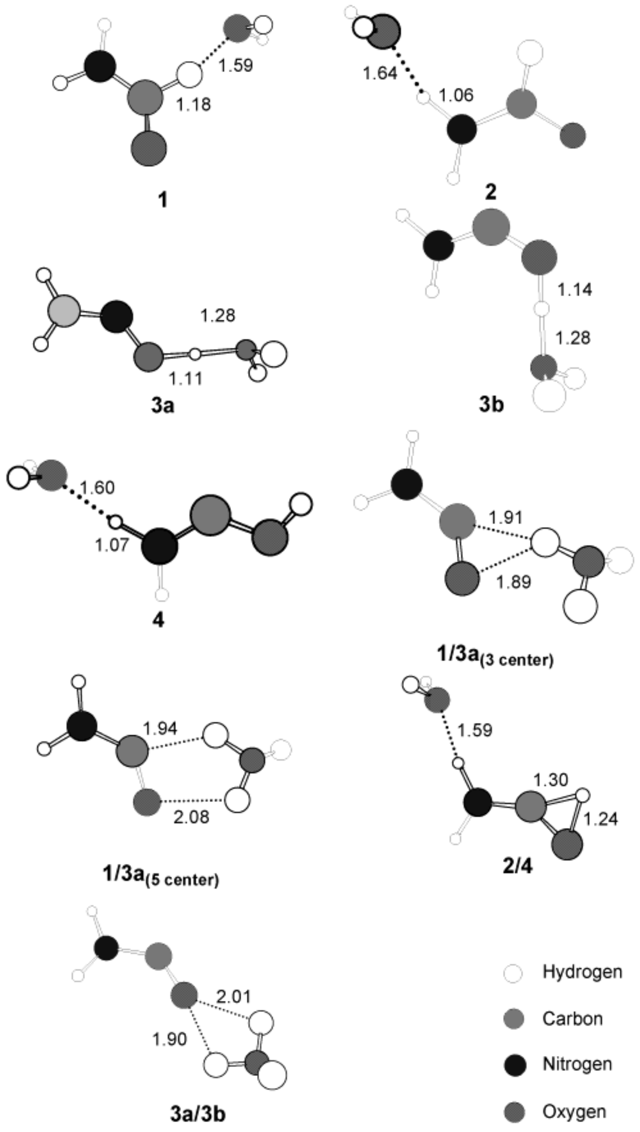


Figure 5. Structures **1**−**4** and the associated transition states involved in the water-catalyzed isomerization of ionized formamide into its carbene isomer. Distances reported on the structures are in angstroms.

the complexes with the water molecule weakly bound to the amino group hydrogens (**2** and **4**). The barrier was calculated to be 13.8 kcal mol^{-1} relative to (**FAm**$^{\bullet+}$ + H_2O) for **2**/**2** and 7.9 kcal mol^{-1} for **4**/**4**, in agreement with the absence of any observed H/D exchange on the amino groups for both isomers.

The reaction with water of the third $COH_3N^{\bullet+}$ isomer, namely the imidic acid[15] HN═CHOH$^{\bullet+}$, was also briefly investigated. The reaction leads to the same product ion *m*/*z* 35 as for the other two isomers. However, the logarithmic plot of the relative intensity vs time of *m*/*z* 45 ions is not linear: the rate of decay is smaller at the beginning of the reaction. This behavior can reflect an isomerization of imidic acid ions prior to production of *m*/*z* 35 ions. In line with this assumption, the reaction with D_2O results in some exchange of two hydrogen atoms by deuterium (*m*/*z* 47).

2. Structure of the [NH_3, H_2O]$^{\bullet+}$ Complex. The final state, [NH_3, H_2O]$^{\bullet+}$, is shown, from experiment and calculations, to be ionized ammonia solvated by water. In agreement with previous calculations,[20] at least two stable structures, **a** and **c**, whose interaction energies are very close (about 30 kcal mol^{-1}; Table 3, Figures 6 and 7), correspond to the [NH_3, H_2O]$^{\bullet+}$ product ion. In structure **a**, one hydrogen of ammonia interacts with the oxygen of water. **a** can convert into **b**, in which both moieties are bound by a three-electron bond. The binding energies for three-electron bonds are known to be overestimated by DFT-based methods.[21] The relative stabilities of **a** and **b** (Table 3) are in agreement with these results: **b** is 9.1 kcal mol^{-1} less stable than **a** at the G3(MP2)//B3LYP level but only 2.7 kcal mol^{-1} at the B3LYP/6-31G* level. No minimum is found at the HF/6-31G* level of calculation, but a shallow minimum was located on the way from **a** to **c** at both the MP2/6-31G* and QCISD/6-31G* levels. In this latter, binding occurs by electrostatic interaction between the water molecule and both a nitrogen atom and a hydrogen atom of the $NH_3^{\bullet+}$ moiety. Structure **c** is significantly different and corresponds in fact to a [NH_4^+, $OH^\bullet$] structure (Figure 7). **b**/**c** is an important energy barrier that explains the very slow rate (efficiency of less than

Table 3. Energies of the Stable States and Transition States of the (Ionized Ammonia, Water) System

	$\Delta E°$ [a]	
	B3LYP/6-31G*	G3(MP2)//B3LYP
$NH_3^{\bullet+} + H_2O$	0.0	0.0
$NH_4^+ + OH^\bullet$	−12.6	−5.5
a	−28.5	−21.7
b	−25.8	−12.6
c	−27.7	−16.9
b/c	−9.7	9.7

[a] Energies in kcal mol^{-1} are relative to $NH_3^{\bullet+} + H_2O$.

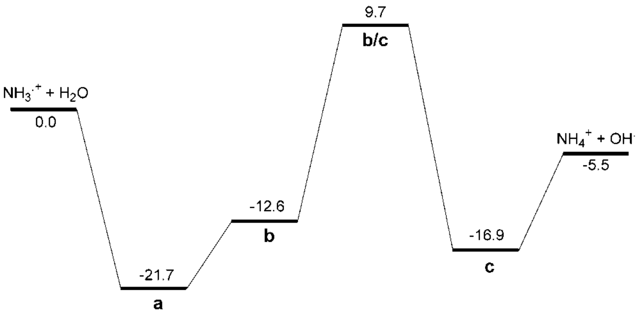


Figure 6. Potential energy surface of the (ionized ammonia, water) system calculated at the G3(MP2)//B3LYP level of the theory (kcal mol^{-1}). The corresponding structures are reported in Figure 7.

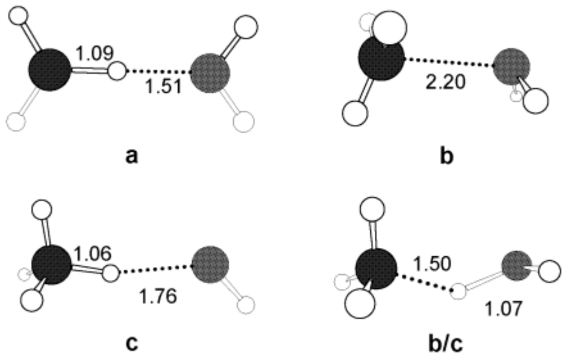


Figure 7. Structures **a**, **b**, and **c** and transition state **b**/**c**. Distances are in angstroms; atom fillings are those of Figure 5.

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(20) (a) Sodupe. M.; Oliva, A.; Bertran, J. *J. Am. Chem. Soc.* **1994**, *116*, 8249. (b) Tachibana, A.; Kawauchi, S.; Nakamura, K.; Inaba, H. *Int. J. Quantum Chem.* **1996**, *57*, 673−682.

(21) Sodupe, M.; Bertran, J.; Rodríguez-Santiago, L.; Baerends, E. J. *J. Phys. Chem. A* **1999**, *103*, 166.

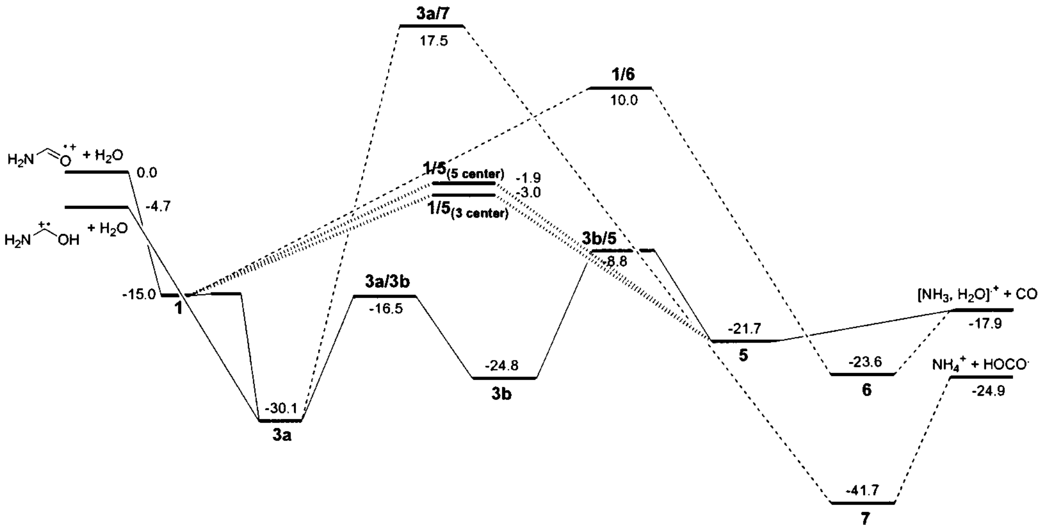

Figure 8. Potential energy surface of the reaction of ionized formamide and its carbene isomer with water, leading to decarbonylation calculated at the G3(MP2)//B3LYP level of the theory (in kcal mol^{-1}). Full lines indicate pathways that are open for both isomers. In hashed lines is a pathway accessible only to the **FAm**$^{•+}$ isomer. In dashed lines are pathways prohibited for the reaction due to a transition state higher in energy than the reactants. The corresponding structures are reported in Figures 5 and 9.

0.01) of production of NH_4^+ in the reaction of ionized ammonia with water[22] and prevents any conversion from **a** to **c** unless the energy excess of the process leading to **a** is higher than 31.4 kcal mol^{-1} (Figure 6). Furthermore, the energy profile clearly indicates that the dissociation of **a** would yield $NH_3^{•+}$ and that of **c** would yield NH_4^+. Since the $[NH_3, H_2O]^{•+}$ product ion, formed by reaction of **FAm**$^{•+}$ and **CAm**$^{•+}$ with water, only yields $NH_3^{•+}$ upon collisions, it allows one to conclude that this product ion corresponds to the structure **a**. Worthwhile to note, NH_4^+ is never observed as a fragment, whatever the residence time of the complex **a** in the presence of water. This means that, in this case, water is unable to lower the transition state enough to lead to complex **c**.

The bimolecular reactions of $[NH_3^{•+}, H_2O]$ as described further below also confirm the structure of the complex. For instance, reaction with CS_2 leads to formation of $[NH_3, CS_2]^{•+}$ by exchange of the water molecule and not by the exchange of $OH^•$ (eq 4).

$$[NH_3^{•+}, H_2O] + CS_2 \rightarrow [NH_3, CS_2]^{•+} + H_2O \qquad (4)$$

3. Catalyzed Processes Leading to the Amide Bond Cleavage. Two steps, catalyzed by the molecule of water, are involved in the amide bond cleavage leading to CO loss. The first one is a proton transport isomerizing **1** and **3a** into a $[H_5NO, CO]^{•+}$ intermediate. The second is the stabilization of the final state.

Since the $[NH_3, H_2O]^{•+}$ product ion possesses the structure **a**, ions **5** and **6** possessing the structure $[H_2O\cdots HNH_2\cdots CO^{•+}]$ (Figures 8 and 9) are the best candidates to be the intermediates in the reaction process, since their simple cleavage, leading to CO loss, yields **a** and not **c**. Considering that **1** and **3a** interconvert, two pathways are possible to reach **5**.

(i) In pathway I, **1** and **5** are connected by a three-member as well as by a five-member transition state, **1/5**$_{(3\ center)}$ and **1/5**$_{(5\ center)}$, both of whose energies lie above that of the initial state **CAm**$^{•+}$ + H_2O but below that of the initial state **FAm**$^{•+}$ + H_2O (Figure 8, hashed line).

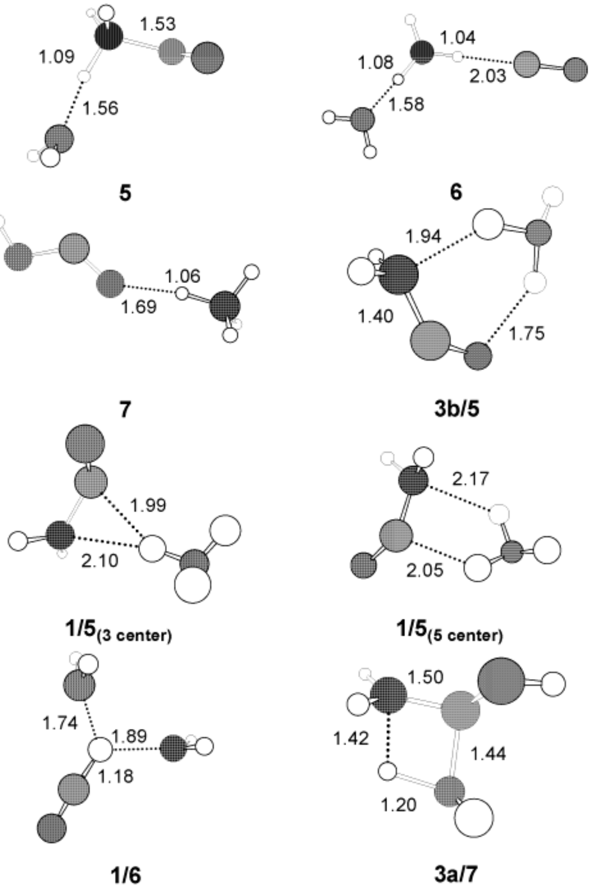

Figure 9. Structures **5**−**7** and associated transition states involved in the water-catalyzed amide bond cleavage. Distances are in angstroms; atom fillings are those of Figure 5.

(ii) In pathway II, **3a** and **5** are connected, after an easy conformation change through **3b**, by the six-membered transition state **3b/5**, whose energy is 4.2 kcal mol^{-1} under that of the (**CAm**$^{•+}$ + H_2O) initial state (Figure 8).

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(22) Adams, N. G.; Smith, D.; Paulson, J. F. *J. Chem. Phys.* **1980**, *72*, 288.

From the energy profile, it is concluded that the pathway II may operate in the reaction mechanism and that this pathway may be irreversible since **3b/5** is, in energy, above that of the final state (**a** + CO) formed by simple cleavage of **5**. The results reported above for the reaction with D_2O are in line with this irreversibility. Effectively, the interconversion between **1** (or **3**) and **5** would lead, after successive reactions with D_2O, to the exchange of three hydrogens, leading to an *m*/*z* 48 ion. This is in contradiction with experiment, which shows that only one H is exchanged, giving *m*/*z* 46.

To confirm that pathway II is operative, it was necessary to determine the final position of the deuterium atoms in the products arising from the reaction of **FAm**$^{\bullet+}$ and **CAm**$^{\bullet+}$ (*m*/*z* 45) with D_2O. From the complexes formed, two competing reactions take place. On one hand, as shown above, the more energetic complexes can dissociate after H/D-exchange to yield *m*/*z* 46 ions possessing the carbene structure. On the other hand, the complexes can isomerize, after internal H/D-exchanges, into complexes **5** containing two deuterium atoms. These complexes undergo decarbonylation to give *m*/*z* 37 product ions, whose CID show that they correspond to a mixture of $[NH_2D, HDO]^{\bullet+}$ and $[NH_3, D_2O]^{\bullet+}$. A branching ratio of 2/1, measured as described in the next paragraph, was found for the formation of $[NH_2D, HDO]^{\bullet+}$ and $[NH_3, D_2O]^{\bullet+}$. Considering now that the isomerization converting **1** (and **3**) into **5** is irreversible, only one hydrogen of **FAm**$^{\bullet+}$ and **CAm**$^{\bullet+}$ is involved in the exchange with a D_2O molecule prior to isomerization in **5**. In this hypothesis, the final products $[NH_3, OD_2]^{\bullet+}$, $[NH_2D, OHD]^{\bullet+}$, and $[NHD_2, H_2O]^{\bullet+}$ are expected to be in a 1/2/0 ratio, which corresponds to the experimental result.

The measurement of the branching ration between $[NH_2D, HDO]^{\bullet+}$ and $[NH_3, D_2O]^{\bullet+}$ is not straightforward to obtain from CID experiments. The relative abundances of $NH_2D^{\bullet+}$ and $NH_3^{\bullet+}$ obtained upon CID have to be corrected by taking in account two phenomena. The first one is the purity of D_2O once introduced in the vacuum chamber, which has been measured by its self−CI reaction in the cell prior to introduction of other reagents. The second one is to take in account the rapid ligand switching of $[NH_2D, HDO]^{\bullet+}$ with D_2O, which gives $[NH_2D, D_2O]^{\bullet+}$ product ions *m*/*z* 38, which are identical to the ions coming from the reaction of the monodeuterated ions *m*/*z* 46. Therefore, the experiment was performed with continuous ejection of *m*/*z* 46 ions. This gives the amount of the *m*/*z* 38 ions coming from the ligand exchange, which has to be added together with the *m*/*z* 37 ions, giving $NH_2D^{\bullet+}$ upon CID. After these corrections, the result is that $[NH_2D, HDO]^{\bullet+}$ and $[NH_3, D_2O]^{\bullet+}$ are formed in a 2/1 ratio.

4. Comparison of the Unimolecular Pathway versus the Bimolecular Pathway. In unimolecular metastable dissociation experiments, $H^{\bullet}$ loss is the unique product of the decomposition of **FAm**$^{\bullet+}$ and one of the products in the decomposition of **CAm**$^{\bullet+}$. This channel is not observed in the bimolecular reaction. This mechanism change and the comparison between the potential energy surfaces of the unimolecular (Figure 1) and of the catalyzed reactions (Figures 4 and 8) led to conclusions on the role of the water molecule on the isomerization and the further amide bond cleavage. The differences appear on three elements that will be successively discussed: solvation of stable states, lowering of the barriers, and stabilization of the reaction product.

First, the initial states are strongly stabilized. The complexation energy of **1** from **FAm**$^{\bullet+}$ + H_2O is 15.0 kcal mol^{-1} (Figure 4). By contrast, that of **3** (from **CAm**$^{\bullet+}$ + H_2O) is higher and 25.5 kcal mol^{-1} (Figure 8). This difference can be explained by a much stronger hydrogen bond in the case of a N−H···O bond than in case of a C−H···O bond. The strong proton bound dimers formed by water in the isomerization steps differ: the complexation of $[NH_3^{\bullet+}, H_2O]$ by CO is very weak, being only 5.7 kcal mol^{-1} for complex **6** (Figure 8). This was expected in this case, since the binding energy is mostly electrostatic.

Second, the water molecule is effective in lowering the energy barrier for all of the H transport steps leading to CO loss.

(i) In the isomerization of **FAm**$^{\bullet+}$ into **CAm**$^{\bullet+}$, the preferential formation of the [**CAm**$^{\bullet+}$, H_2O] complex is enhanced by a very low transition state for the 1,2-H transport. The barrier is almost zero, whereas in the unimolecular case, it is 35.4 kcal mol^{-1} (Figures 1 and 4). Therefore, although the two isomers **FAm**$^{\bullet+}$ and **CAm**$^{\bullet+}$ do not interconvert easily in the gas phase, the presence of a single molecule of water, involved in the proton transfer, will drive the reaction forward to the formation of the **CAm**$^{\bullet+}$ ion. By contrast, when the water molecule is only a spectator of the 1,2-H transport, as in **2/4** (Figures 4 and 5), the barrier is almost unchanged (36.4 kcal mol^{-1}) compared to the unimolecular reaction and the only effect of solvation is to contribute to an increase of the internal energy through the solvation energy. Thus efficient catalysis is ensured by strong interactions between the water molecule and the reactive site of the complex.

(ii) In the unimolecular pathway, the lowest energy pathway leading from **FAm**$^{\bullet+}$ to $[OC\cdots NH_3]^{\bullet+}$ is the migration of the entire $NH_2^{\bullet}$ group from the carbon of HCO^+ to the hydrogen atom. This transition state lies 28.4 kcal mol^{-1} above the starting product. The corresponding transition state of the bimolecular pathway (**1/6**) lies 10.1 kcal mol^{-1} above the energy of the initial reactants and the barrier is about 25.1 kcal mol^{-1} above the energy of **1** (Figure 8). The water molecule, acting as a spectator, does not solvate the migrating group. Therefore, this pathway would be too costly to be operative in the bimolecular reaction.

(iii) In the unimolecular system, the second lowest energy pathway for the loss of CO is a direct 1,2-H transport leading from **FAm**$^{\bullet+}$ to $H_3N^{+-}C^{\bullet}{=}O$, the barrier for which is 47.9 kcal mol^{-1} above the energy of the reactant ion. The analogous bimolecular pathway, pathway I (Figure 8, hashed lines), could be effective in the case of ionized formamide but only as a minor channel. In this case, the barrier **1/5** lies 12.0 kcal mol^{-1} above the energy of complex **1**, only slightly lower than the entry point. Thus water solvation has lowered this 1,2-H transfer barrier by about 36 kcal mol^{-1}.

(iv) By contrast, the unimolecular analogue of pathway II proceeds through a 35.4 kcal mol^{-1} barrier for a 1,2-H transfer from **FAm**$^{\bullet+}$ to **CAm**$^{\bullet+}$, followed by a high 57.0 kcal mol^{-1} barrier for a 1,3-H transfer from **CAm**$^{\bullet+}$ to $H_3NCO^{\bullet+}$. These barriers explain that metastable **CAm**$^{\bullet+}$ loses CO via isomerization into **FAm**$^{\bullet+}$[9b] (Figure 1). The equivalent barriers for the bimolecular pathway are nearly nonexistent for the first 1,2-H transport step and only 21.3 kcal mol^{-1} above the energy of **3a** for the 1,3-H transport step (**3b/5**, Figure 8). Therefore, solvation by a water molecule produces a complete change in the reaction channels, where the lower energy channels involve the water molecule assisting the transport of proton from one site to the other.

The third effect of solvation is the stabilization of the reaction product: it is only because of the very high solvation energy of ionized ammonia by water (21.7 kcal mol^{-1}, Figure 6) that the CO loss could at all be observed. Formation of ionized ammonia plus water and carbon monoxide would be endothermic by 3.8 kcal mol^{-1} relative to the **FAm**$^{\bullet+}$ + H_2O entry point and is therefore not observed.

5. Bimolecular Reactivity of the $[H_2NH\cdots OH_2]^{\bullet+}$ Product Ion. It is, to our knowledge, the first time that this ion is generated. Therefore, no experimental data exist on its chemical properties. First results indicate that its behavior is completely different of that of the $[H_2O, H_2O]^{\bullet+}$ dimer studied by Nibbering et al.,[23] who have measured the EI and the acidity of this ion. It has not been possible to carry out a similar study on the $[NH_3, H_2O]^{\bullet+}$ system since, in the presence of neutral molecules, this ion reacts more often by ligand exchange while the charge exchange reactions are rare as well as reactions leading to the protonation of the neutral reagent. This facile substitution of the water molecule by the neutral reagent may be due to the strongly dissymmetric repartition of the charge between the two moieties of the ion. In a first ligand exchange step, complexes such as $[NH_3, CS_2]^{\bullet+}$, $[NH_3, \text{alkene}]^{\bullet+}$, $[NH_3, \text{benzene}]^{\bullet+}$, and $[NH_3, \text{alcohol}]^{\bullet+}$ are readily formed. These complexes can remain as ammonia-solvated ions but can also collapse and form a covalent bond or lead to further reactions.

For instance, in the presence of ethylene, $[NH_3, H_2O]^{\bullet+}$ leads to the $[NH_3, CH_2{=}CH_2]^{\bullet+}$ complex, which collapses to form a covalent bond. This is shown by the CID spectrum of the $C_2NH_7^{\bullet+}$ ion formed, which is identical to that of the $^{\bullet}CH_2CH_2NH_3^{+}$ distonic ion prepared by fragmentation of ionized decylamine.

The $[NH_3, CH_3OH]^{\bullet+}$ complex, formed by ligand exchange with methanol, yields NH_4^+ upon collision. The $[NH_3, CD_3OH]^{\bullet+}$ dimer, formed by ion–molecule reaction from the $[NH_3, H_2O]^{\bullet+}$, only leads upon collision to NH_3D^+, in contrast with the vertical ionization of $[NH_3, CH_3OH]$ clusters,[24] suggesting different intermediates in both processes.

6. Related Systems. In the previous section, it was shown that the bimolecular reaction of $[NH_3, H_2O]^{\bullet+}$ with methanol leads to the formation of the $[NH_3, CH_3OH]^{\bullet+}$ complex. It would be interesting to see whether this complex could be formed by the reaction of methanol with ionized formamide or with its carbene isomer. These reactions result in a dominating proton transfer (*m*/*z* 33, 70%), along with the formation of NH_4^+ (30%). The proton transfer is the consequence of the higher proton affinity of methanol (180.3 kcal mol^{-1}).[18] The formation of NH_4^+ was proved to be a secondary process, as it is nearly suppressed upon strong continuous irradiation at the exact mass of $[NH_3, CH_3OH]^{\bullet+}$ (*m*/*z* 49). V_{p-p} of the rf irradiating field was set to 300 V, corresponding to an ejection time of 70 μs.[25] Such a procedure would eject these ions if they are transiently formed and have a sufficiently long lifetime. This demonstrates that most of the initial NH_4^+ product ions are in fact produced through an intermediate $[NH_3, CH_3OH]^{\bullet+}$ complex, corresponding to a loss of CO from the encounter complex, as for the reaction with water. However, they are produced, in this case, with enough internal energy to decompose in a short time frame and, therefore, are barely detectable in the reaction.

Ionized formic acid $HCOOH^{\bullet+}$ and its carbene isomer $HO{-}C{-}OH^{\bullet+}$, which is also more stable,[14] react with water at collision rate and in the same way. Formation of H_3O^+ is the main reaction observed. However, the formation of water dimer radical cation is also observed for about 5–10%. It is formed, as for **FAm**$^{\bullet+}$, by catalyzed loss of CO from the reacting complex. The reaction with $^{18}OH_2$ confirms that the oxygen lost in the CO moiety originates from the initial ion, and no oxygen exchange is observed. Continuous fast ejection of the water dimer radical cation does not reduce significantly the amount of protonated water, which means that formation of H_3O^+ occurs mainly directly or through an intermediate having a very short lifetime. The importance of the direct protonation of water is in agreement with the greater acidities of $HO{-}C{-}OH^{\bullet+}$ $[PA_O(OCOH^{\bullet})^{26} = 145$ kcal mol$^{-1}]$ and $HCOOH^{\bullet+}$ $[PA_C(OCOH^{\bullet})^{14,26} = 141$ kcal mol$^{-1}]$ compared to those of **FAm**$^{\bullet+}$ and **CAm**$^{\bullet+}$. As a consequence, in the intermediate complexes, some of which have been calculated,[26] the proton is more likely to be bound to water $[PA(H_2O)^{18} = 165.2$ kcal mol$^{-1}]$ than to the radical moiety. By performing the reaction with $HCOOD^{\bullet+}$ (*m*/*z* 47), formation of H_3O^+ and H_2DO^+ occurs in a 1:1 ratio, as observed at the beginning of the reaction ($t = 0.4$ s, $P = 1.2 \times 10^{-8}$ mbar) and before further H/D exchanges of the oxonium ions with water (eq 5).

$$\begin{aligned} &HCOOD^{\bullet+} + H_2O \rightarrow [H_2O, HOCOD^{\bullet+}] \\ &\qquad \rightarrow [HO{-}C{-}O\cdots DOH_2]^{\bullet+} \rightarrow HOC{=}O + H_2DO^+ \\ &\qquad \rightarrow [DO{-}C{-}O\cdots HOH_2]^{\bullet+} \rightarrow DOC{=}O + H_3O^+ \end{aligned} \tag{5}$$

This indicates that the ionized formic acid undergoes a water-assisted isomerization into its more stable carbene isomer prior to protonation of water. The structure of the hot complex between ionized carbene and water is likely to be $[H_3O^+, OCOH^{\bullet}]$, and direct fragmentation leads to protonated water. This explains the near unit efficiency of the reaction forming either H_3O^+ or the $[H_2O, H_2O]^{\bullet+}$ dimer. Therefore, no back-dissociation into the carbene ion is observed and the isomerization could not be evidenced by reaction with cyclopropane. For the same reason, no significant H/D exchange on the initial *m*/*z* 47 $HCOOD^{\bullet+}$ ion is observed.

In contrast with the formamide and formic acid, ionized acetaldehyde $CH_3\text{-}CHO^{\bullet+}$ is more stable than its carbene counterpart $CH_3\text{-}COH^{\bullet+}$, but the solvated carbene is generally more stable than the solvated acetaldehyde ion. Catalyzed isomerization of $CH_3\text{-}CHO^{\bullet+}$ into its enol $CH_2{=}CHOH^{\bullet+}$ has been studied.[6f] It has been shown that interaction of $CH_3\text{-}CHO^{\bullet+}$ with methanol yields two complexes. The first one, $[CH_3(H)O\cdots HCH_2\text{-}CHO]^{\bullet+}$, operates in the catalyzed 1,3-H^+, leading to isomerization (eq 6).

$$\begin{aligned} &[CH_3(H)O\cdots HCH_2{\_}CHO]^{\bullet+} \rightarrow \\ &\qquad [CH_3(H)O\cdots HOCH{=}CH_2]^{\bullet+} \rightarrow \\ &\qquad\qquad CH_2{=}CHOH^{\bullet+} + CH_3OH \end{aligned} \tag{6}$$

It has been previously proposed that the second one, $[CH_3(H)O\cdots H(O)C{-}CH_3]^{\bullet+}$, interconverts with the solvated carbene

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[23] de Visser, S. P.; de Koning, L.; Nibbering, N. M. M. *J. Phys. Chem.* **1995**, *99*, 15444.

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[26] Hrušák, J.; McGibbon, G. A.; Schwarz, H.; Terlouw, J. K. *Int. J. Mass Spectrom. Ion Processes* **1997**, *160*, 117.

$[CH_3(H)O\cdots HO-C-CH_3]^{\bullet+}$ prior to formation of protonated methanol (eq 7).

$$[CH_3(H)O\cdots H(O)C-CH_3]^{\bullet+} \rightarrow [CH_3(H)O\cdots HO-C-CH_3]^{\bullet+} \rightarrow CH_3OH_2^{+} + CH_3CO^{\bullet} \quad (7)$$

Revisiting this system, the reaction of CH_3-$COH^{\bullet+}$ with methanol was performed. The only reaction observed is protonation of methanol, in agreement with the energy profile.[6f]

The reaction of CH_3-$C-OH^{\bullet+}$ with H_2O is completely different, since the PA of water lies below those of the $CH_3CO^{\bullet}$ radical: protonation does not take place. In this case, interconversion between solvated carbene and solvated CH_3-$CHO^{\bullet+}$ is the most favored reaction (eq 8).

$$[H_2O\cdots HO-C-CH_3]^{\bullet+} \rightleftarrows [H_2O\cdots H(O)C-CH_3]^{\bullet+} \rightarrow CH_3\text{-}CHO^{\bullet+} + H_2O \quad (8)$$

In the presence of D_2O, the consequence of interconversion is the exchange of the hydroxylic hydrogen of the ion with those of water, which leads to a shift of the initial reactant ion from *m*/*z* 44 to 45. Reaction of cyclopropane indicates that the so-formed *m*/*z* 45 ion no longer has the carbene structure (no $CH_2^{\bullet}$ transfer to the ion) and therefore most likely possesses the CH_3-$CDO^{\bullet+}$ structure.

Conclusion

The reaction of ionized formamide with water can be viewed as a prototype for water-assisted amide bond cleavage. The exclusive and abundant loss of CO observed for this system contrasts with the unimolecular reactivity of formamide ions, which do not undergo decarbonylation in the metastable energy frame. In contrast, it is known[9b] that the unimolecular loss of CO observed for the metastable isomeric carbene $HOCNH_2^{\bullet+}$ is fairly abundant and occurs via a rearrangement into the formamide structure (Figure 1).

A reverse situation was encountered when a molecule of water is added to the system: both isomeric ions react in the same way, but it was shown that a catalyzed isomerization of formamide ions into carbene ions occurs prior to CO loss. This result and those attained on related systems are new examples of catalyzed 1,2-H^+ transfers that can be barrier free. This isomerization of a conventional radical cation into its carbene isomer was unambiguously proved by means of an unprecedented and quite general characteristic reaction of cyclopropane, which transfers specifically a methylene to a number of ionized carbenes and not to their isomers.

The several cases of 1,3-H^+ transport observed in this work confirm the precedent studies,[6] showing that even though the catalysis does strongly reduce the energy barriers and opens new pathways to be operative, the energy barrier remains nonnegligible.

In the case of the formamide ion/water system, water was shown to catalyze all steps of the reactions pathways, including the final amide bond cleavage leading to the $[NH_3^{\bullet+}, H_2O]$ stable complex. This ion, prepared for the first time in this work, is the ammonia radical cation solvated by water, which can, as a weakly bonded complex, undergo a number of new bimolecular reactions such as ligand exchanges or covalent bond formation. This opens a very attractive field of study, allowing the preparation of unprecedented ionized complexes, such as $[NH_3, CH_3OH]^{\bullet+}$, or distonic ions and related species, which are often difficult to obtain by more classical means.

Supporting Information Available: Cartesian coordinates of all the optimized stable state and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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