Peptide Bonds in the Interstellar Medium: Facile Catalytic Formation from Nitriles on Water–Ice Grains

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ABSTRACT: A recent suggestion that acetamide, CH₃C(O)NH₂, could be readily formed on water–ice grains by the acid induced addition of water across the C≡N bond has now been shown to be credible. Computational modeling of the reaction between R−CN (R = H, CH₃) and a cluster of 32 molecules of water and one H₂O⁺ proceeds catalytically to form first a hydroxy imine R−C(OH)−NH and second an amide R−C(O)NH₂. Quantum mechanical tunneling, computed from small-curvature estimates, plays a key role in the rates of these reactions. This work represents the first reasonable effort to show, in general, how amides can be formed from nitriles and water, which are abundant substrates, reacting on a water–ice cluster containing catalytic amounts of hydrons in the interstellar medium with consequential implications toward the origins of life.

INTRODUCTION

The so-called peptide bond, −C(O)NH−, which is found in amides connects amino acids to peptides—of paramount importance to present day life on Earth. Unsurprisingly, how, when, and where peptide bond formation arose is of immediate interest in prebiotic astrochemistry, tackling that challenging question: the origins of life.¹,²

The simplest amides, formamide, HC(O)NH₂, and acetamide, CH₃C(O)NH₂, are common constituents of star-forming regions in our galaxy.³,⁴ but apparently protonamide, CH₃CH₂C(O)NH₂ is not.⁵ Adande et al.⁶ have shown, based on their observations of formamide toward star-forming regions of dense molecular clouds, that the compound could have been brought to Earth by exogenous delivery in substantial amounts of ~0.18 mmol m⁻² in a single impact.

The formation routes to formamide are still unclear; some have suggested gas-phase pathways via formaldehyde and amido nitrogen.⁶,⁷

H₂CO + NH₃* → HCONH₂ + H⁺

but disputed by Song and Kästner⁸ and convincingly refuted by Douglas et al.⁹ or surface reactions ¹⁰ by the hydrogenation of isocyanic acid, HNCO, and on carbon monoxide–ammonia ices:¹¹

NH₃ → NH₂* + H⁺  (1)

H⁺ + CO → HCO*  (2)

HCO* + NH₂* → HC(O)NH₂  (3)

and more recently by metal-ion mediated substitution reactions:¹²

HC(O)X + NH₃ → HC(O)NH₂ + X

where M = Na⁺, K⁺, Mg⁺, Mg²⁺, and Al⁺ and X = H, OH, and CH₂OH but the evidence for all these is underwhelming. A comprehensive summary has been given recently by Chuang et al.¹³ during the course of their laboratory work on the formation of formamide in water- and carbon monoxide-rich water ices with ammonia as the substrate. Vacuum ultraviolet (VUV) irradiation of water-rich and CO-rich ammonia ices at 10 K with compositions H₂O:CO:NH₃ = 10:5:1, CO:NH₃ = 4:1 and CO:NH₃ = 0.6:1 have shown that formamide is preferentially formed, although mechanistically the situation is complicated with no clear indication as to actual formation routes.¹³ Indirect evidence for the formation routes of formamide based on the stratified distribution of the molecules HNCO and H₂CO, putative parents of HCONH₂, in the atmosphere of the HH 212 protostellar disk, appears to rule out HNCO as a parent.¹⁴

Most recently Marks et al. have carried out experiments involving acetaldehyde (ethanal) ammonia mixtures undergoing irradiation with simulated galactic cosmic rays.¹⁵ They report

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the formation of glycinal, HC(O)CH₂NH₂, and acetamide and their tautomers HC(OH)CHNH₃ and H₂C=C(OH)NH₂. The compounds arise, they suggest, as the result of barrierless radical–radical recombination reactions:

\[ \text{HC(O)CH}_2^* + \text{NH}_2 \rightarrow \text{HC(O)CH}_2\text{NH}_2 \]
\[ \text{CH}_3\text{C(O)}^* + \text{NH}_2 \rightarrow \text{CH}_3\text{C(O)NH}_2 \]

This is somewhat surprising since tautomerization of acetamide would normally be expected to lead to the imidic acid CH₂C(OH)NH--+NH.

Studies of comets have indicated that the early Solar Nebula had nitriles (cyanides) such as HCN and CH₃CN in abundance. It is currently assumed that reactions in the bulk or on the surface of water–ice grains are the most likely formation routes for complex organic molecules which are then liberated into the gas-phase by UV irradiation, electron and cosmic ray bombardment, via thermal shocks or grain–grain collisions.\[16\]–[20]

In a computational study of the direct reaction HC≡N + H₂O → HCN(H)≡NH neither the presence of a second H₂O as a catalyst or as a spectator or as a reactant was sufficient to reduce the high barriers encountered, in excess of 220 kJ mol⁻¹, which thereby rule out the possibility of it occurring in cold molecular clouds.\[21\] The most pertinent previous work simulated a 33 H₂O molecule cluster and showed that HC≡N cannot react with HCN(H)≡NH under interstellar ice conditions because of large energy barriers. Any reactivity that was feasible proceeded through the CN⁺ radical.\[22\] These studies are in accord with the statement that “nitriles are curious functional groups because they are kinetically rather inert while thermodynamically quite unstable.”\[23\]

Ultraviolet (UV) photolysis of water methyl cyanide ices at 20 K (H₂O:CH₃CN = 20:1) does give rise to the formation of CH₃C(O)NH₂ and its isomer N-methyl formamide CH₃NHCHO, but many other products as well.\[24\]

A consideration of the various suggested reactions in the literature led one of us to suggest that H₂O⁺ induced water addition to nitriles on water–ice grains was likely to provide the most probable route.\[25\] It is known that H₂O⁺ exists in the ISM and even in other galaxies, that it reacts in water–ices, and that it has the potential to drive subsequent reaction.\[26\]–[29] Note that although there is no direct experimental spectroscopic evidence for the presence of H⁺ in the ISM, our own Sun emits a “solar wind” of particles which are 95% H⁺ and 4% He\[30\]. In addition “cosmic rays” mainly consist of high-energy protons. The capture of H⁺ by a water–ice grain in a one-time event would provide the necessary acid functionality.

Woon has very recently reviewed what is known about cation reactions in ices from quantum chemical cluster studies, highlighting the novel and more efficient pathways, vis-à-vis the gas-phase, that HCO⁺, CH₃⁺, and C⁺ (but not H₂O⁺) undergo and appealed for experimental confirmation.\[30\]

Laboratory experiments have shown that bombardment of water ice samples on a copper substrate at 10 K by 60 keV O⁶⁺ ions yields a number of secondary ions including (H₂O)ₙ⁺H⁺ with \( n \approx 1 \rightarrow 8 \), although these ions are perhaps more accurately denoted as (H₂O)ₙ⁻¹H₂O⁺.\[31\] The production efficiency is much lower when crystalline ice is bombarded in comparison with amorphous ice.

There is little direct evidence for the charge state of a typical water–ice grain; laboratory experiments of necessity greatly enhance molecular synthesis during electron bombardment of ices, thus preface negatively charging the sample. For example, 1 keV electron irradiation of a 1:1 mixture of ammonia and methanol at 30 K led to the formation of formamide, formic acid, methyl formate, formaldehyde, and carbon monoxide and dioxide, as well as methane, but the electron flux is some 10⁶ times greater than the sample would experience in a cold dense molecular cloud.\[32\] For the purposes of this work, we assume that the water–ice is neutral and acquires a positive charge on a one-time capture of H⁺ or indeed H₂O⁺.

A primary consideration for suggesting acidified amorphous water–ice is the high mobility of the proton through the lattice; the transfer mechanism, via Grothuss hops, takes place on a subpicosecond time scale and with barriers of \( \approx 1 \) kJ mol⁻¹—these effectively increase the “collision rate” or encounter between reactant and H₂O⁻.\[20\]–[33] Since the proton is so free to move throughout the cluster, its actual location on the surface or in the interior, which is sometimes a consideration in discussions of reactions on water–ice grains, is much less relevant here. Note too that the diffusion of radicals on/in water–ice grains is likely to be very much slower.

The first step in the proposed addition of water is the protonation at nitrogen of the nitrile to form RC≡NH⁻ and in the case of HCN to form iminomethylum, HC≡NH⁻; this species has been widely detected in star-forming regions\[34\]–[36] and in Titan’s atmosphere.\[37\] Although it had been characterized as a precursor of HC≡N, in the most recent observations Fontani et al. show that it is formed from HC≡N or HC≡N⁺.\[38\]

Fundamental laboratory work to characterize the spectroscopic parameters for CH₃C≡NH⁻ have been carried out but interstellar searches have not so far been successful.\[39\]

The hydronium-induced addition of water was seen as a two-step process with the first forming hydroxy imines or imidic acids RC(OH)⁻=NH and the second converting these to amides RC(O)NH₂; the latter reaction can occur either by intramolecular hydrogen-transfer via quantum-mechanical tunneling or by the further protonation of the nitrogen-atom followed by deprotonation from the O atom.

The actual formation of peptides as a byproduct was observed\[40\] after the deposition of C atoms onto a CO + NH₃ ice at 10 K and subsequent warming to 300 K. The authors argue that the initial reaction product is aminoketene, H₂NCH₃=CH⁻=O, which polymerizes on warming yielding (−CH₂−C(O)=NH−)ₙ chains. While the experiments are compelling, the conditions are somewhat artificial since they consider pure CO + NH₃ ices with substantial quantities of carbon atoms. The initial step H₂N + C(³P₂) → H₃N−C is highly exothermic, \( ΔH = -103 \) kJ mol⁻¹, this is followed by a 1,2-H-transfer to H₃N−C=H and finally reaction with CO to H₃N−CH=CH=C=O.

Interestingly Canepa\[41\] in considering the survival rates of glycine, NH₂CH₂C(O)OH, embedded in micrometeorites undergoing atmospheric re-entry has shown that aminoketene, the product of dehydration, would also survive.

In this paper, we focus on a solid-state chemistry formation mechanism of R−C(OH)⁻=NH and subsequently R−C(O)⁻=NH₂. We perform electronic structure investigations of the energetics and also thermal rate constants calculations of this reaction mechanism. This information can then be used in astrochemical modeling and may prompt experimental laboratory confirmation.

**METHODS**

Calculations were performed with the program Gaussian\[42\] and used the long-range dispersion corrected density functional
oB97X-D together with the triple \( \zeta \) basis set with added polarization and diffuse functions 6-311++G(d,p) with a factor of 0.96 applied to scale the zero-point energy. The functional is known as a range-separated hybrid generalized gradient approximation functional and is capable of modeling both short- and long-range interactions using a version of Grimme’s D2 dispersion treatment. The use of higher level theory for modeling a system with \( \approx35 \) “heavy” atoms would have exceeded our computational resources.

A system with thirty-two water molecules and one hydronium ion, \( \text{H}_3\text{O}^+ \), based on a cluster originally designed by Rimola et al.,\(^{46} \) with a total “volume” of \( \approx2,600 \text{ Å}^3 \), was chosen together with one reactant, either HCN or \( \text{CH}_3\text{CN} \). This choice represents a compromise between realistic ISM concentrations and computational effort, Figure 1.

![Figure 1. HCN embedded in acidified water.](image)

All structures, the largest of which:

\[
[\text{CH}_3\text{C} \equiv \text{N}-32\text{H}_2\text{O}-\text{H}_3\text{O}^+],
\]

were fully optimized, and the harmonic frequencies were computed using DFT. Frequency calculations were performed in order to verify that all intermediates are true minima on the potential energy surface and that all transition states exhibit a single imaginary frequency. We studied all species in the reaction mechanism with the unrestricted \( \omega\text{B97XD}/6-311++G(d,p) \) model chemistry. Gaussian 16 automatically includes an ultrafine integration grid in the DFT calculations in order to improve the accuracy of the results. The grid greatly enhances the accuracy at reasonable additional cost.

The reaction paths are computed using the intrinsic reaction coordinate (IRC) methodology\(^{37,46} \) to confirm the identities of the reactants and products for every transition state. IRC calculations require initial force constants of the transition state. Then, the first and second order energy derivatives are obtained to calculate the projected harmonic vibrational frequencies along each reaction path. The minimum energy paths (MEPs) were computed using the Page–MclIver integrator with a gradient step size of 0.1 \( \text{a_0} \).\(^{49} \)

Small curvature quantum mechanical and quantized-reactant-states tunneling calculations\(^{50,51} \) employed the PILGRIM software suite\(^{52} \) for the computation of rate constants via transition state theory\(^{53} \) (TST) and variational\(^{54} \) TST (VTST) necessitating calculations along the minimum energy path.

**RESULTS**

Prior to the first reaction steps we begin by considering a previously published\(^{46} \) cluster of 33 water molecules, \([33-(\text{H}_2\text{O})]\), to which a low energy Hydron \( \text{H}^+ \) is added in a highly exothermic process, \( \Delta H^\circ(0 \text{ K}) = -1,065 \text{ kJ mol}^{-1} \); this in turn can be dissipated throughout the cluster and/or serves to drive subsequent reactions. Although the whole process of energy dissipation is poorly understood Ferrero et al.\(^{55} \) have shown in \( \textit{ab initio} \) molecular dynamics simulations of the reactions

\[
\text{N} + \text{H} \rightarrow \text{NH} \rightarrow \text{NH}_2 \rightarrow \text{NH}_3
\]

on water–ice surfaces that 60–90% of the reaction energy may be absorbed by the ice cluster within 1 ps. If the energy is not dissipated quickly, then the newly formed product will promptly dissociate; if the energy is dissipated too quickly, then there is not enough to drive subsequent reactions.

The only notable difference between the two clusters \([33(\text{H}_2\text{O})]\) and \([33(\text{H}_2\text{O})-(\text{H}^+)\] , which is more realistically depicted as \([32(\text{H}_2\text{O})-(\text{H}^+)\] , are the three additional vibrational modes, two \( \text{O}–\text{H} \) asymmetric stretching vibrations near 2,400 cm\(^{-1} \) and a characteristic symmetric at 2,800 cm\(^{-1} \). It is to this cluster that the reactants HCN and \( \text{CH}_3\text{CN} \) are then added.

**First Step: Imidic Acid Formation.** As originally envisaged the hydrolysis of \( \text{HC}_3\text{N} \) proceeded in three distinct phases:

1. \( \text{HC} \equiv \text{N} + \text{H}_2\text{O}^+ \rightarrow \text{HC} \equiv \text{N}^+ + \text{H}_2\text{O} \)
2. \( \text{HC} \equiv \text{N}^+ + \text{H}_2\text{O} \rightarrow \text{HC} \equiv \text{O}^+ + \text{NH}_2\text{O} \)
3. \( \text{HC} \equiv \text{O}^+ + 32\text{H}_2\text{O} \rightarrow \text{HC} \equiv \text{O}^+ + 3 \text{H}_2\text{O} + 31\text{H}_2\text{O} \)

the exothermic first step \( \Delta H^\circ(0 \text{ K}) = -20.5 \text{ kJ mol}^{-1} \) simply a reflection of the larger proton affinity of HCN of 712.9 kJ mol\(^{-1} \) vis-à-vis \( \text{H}_2\text{O} \) of 691.0 kJ mol\(^{-1} \).\(^{56} \) In a water cluster of an additional 32 \( \text{H}_2\text{O} \) molecules, however, these later steps are elided since as \( \text{H}_2\text{O} \) adds to the C atom it simultaneously transfers H to a neighboring O atom.

Overall reaction 7 is exothermic by \( -83 \text{ kJ mol}^{-1} \), Table 2, which is considerably different from the gas-phase \( \Delta H^\circ(0 \text{ K}) = -21.9 \text{ kJ mol}^{-1} \), reflecting the tighter binding of the hydrolyzed product in comparison to the reactant.

The barrier to reaction 7, that is, protonation at the N atom, in the case of HCN is 78.5 kJ mol\(^{-1} \) and is even lower at 51.9 kJ mol\(^{-1} \) for acetonitrile.

Although Figure 1 shows the actual reaction structure, an oversimplified version, Figure 2, where the scaffold of water molecules has been deleted to highlight the important

![Figure 2. Key elements of the reaction scheme for the first step.](image)
interactions, shows the parts played by four key water molecules. The first is the proton donor $\text{H}_3\text{O}^+$, the second is the “reactant” which will attack the C atom and also transfer a $\text{H}^+$ to the “acceptor” water, while the “companion” $\text{H}_2\text{O}$ is less involved but nevertheless stabilizes the system through $\text{H} \cdots \text{OH}$ hydrogen-bonding; snapshots along the IRC path are shown in Figure 3 to the final product, methanimidic acid in its (E,Z) conformation with respect to the dihedrals $\angle\text{OCNH}$ and $\angle\text{HOCN}$, respectively.

Second Step: Amide Formation. We can distinguish between two different routes from the hydroxy imines to the corresponding amides which can proceed intramolecularly or intermolecularly.

Intramolecular Route. Once the $\alpha$-hydroxy imines, $\text{R}−\text{C(OH)]NH}$, known as methanimidic and ethanimidic acids, are formed, then an intramolecular 1,3-H-transfer leads to formamide or acetamide, respectively; however, the barriers are considerable ranging from 136 or 128 kJ mol$^{-1}$ in the gas-phase to 169 and 142 kJ mol$^{-1}$ in this water-cluster. Clearly, surmounting such barriers is unfeasible at temperatures much less than 300 K except by tunneling.

Note that the presence of additional water molecules makes very little difference in the energetics of the process in comparison to the gas-phase. Exactly the same conclusion can be drawn from the gas-phase work of Darla et al. which showed in $\omega\text{B97xD}/\text{aug-cc-pVTZ}$ calculations that even in the presence of a “catalytic” water molecule the 1,3[H]-transfer faces a barrier of 131 kJ mol$^{-1}$ or 132 kJ mol$^{-1}$ with the additional water present as a “spectator”. The additional water molecules and $\text{H}_2\text{O}$ in our system of $\text{RC}≡\text{N} + 32\text{H}_2\text{O} + \text{H}_3\text{O}^+$ only marginally affect the 1,3[H]-transfer reaction; this is seen in the energetics, as discussed above, and also from the values of the imaginary frequencies which are gas-phase, 2000 and 1,988 cm$^{-1}$, and cluster, 1,953 and 1,916 cm$^{-1}$, for $\text{HC(OH)NH} \leftrightarrow \text{HC(O)NH}_2$ and $\text{CH}_3\text{C(OH)NH} \leftrightarrow \text{CH}_3\text{C(O)NH}_2$, respectively.

In the case of the gas-phase $\text{RC(OH)NH} \leftrightarrow \text{RC(O)NH}_2$ isomerization reaction, PILGRIM$^{57}$ calculations at B3LYP/cc-pVTZ incorporating small-curvature tunneling yields rate constants, $k$, and half-lives, $\tau$, as shown in Table 1; the ice-

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**Table 1. Isomerization Rate Constants**

| $T$/K | $\text{HC(OH)NH} \rightarrow \text{HC(O)NH}_2$ | $\text{CH}_3\text{C(OH)NH} \rightarrow \text{CH}_3\text{C(O)NH}_2$ |
|-------|---------------------------------|---------------------------------|
|       | $k$/s$^{-1}$ | $\tau$/days | $k$/s$^{-1}$ | $\tau$/days |
| 50    | $7.6 \times 10^{-9}$ | 1,060 | $4.4 \times 10^{-9}$ | 180 |
| 100   | $7.8 \times 10^{-9}$ | 1,028 | $8.3 \times 10^{-9}$ | 100 |
| 150   | $1.2 \times 10^{-8}$ | 660 | $2.3 \times 10^{-8}$ | 36 |
| 200   | $4.2 \times 10^{-8}$ | 190 | $9.3 \times 10^{-8}$ | 9 |
| 250   | $3.4 \times 10^{-7}$ | 24 | $6.7 \times 10^{-7}$ | 2 |
| 300   | $4.4 \times 10^{-6}$ | 2 | $7.5 \times 10^{-6}$ | 0.2 |
cluster values are probably not dissimilar. At the lowest temperatures, here ≤ 150 K, quantized reactant states tunneling is included. The barrier to reaction is higher at 131.5 kJ mol\(^{-1}\) for HC(OH)NH\(_2\) compared to the 123.9 kJ mol\(^{-1}\) for CH\(_3\)C(OH)NH\(_2\). Consequently, the rate of isomerization to the appropriate amide is faster for ethanimidic acid. These are substantially faster rates of isomerization than our previous Multiwell values. Figure 4, which were based on Eckart tunneling,\(^{25}\) this makes the intramolecular route competitive with the intermolecular route, discussed below.

![Figure 4](image.png)

**Figure 4.** Rate constants gas-phase tautomerization: Eckart (— — —) versus small-curvature tunneling ( ). CH\(_3\)C(OH)NH (red), HC(OH)NH (black).

A not dis-similar situation is considered by Concepción et al.,\(^{58}\) in their work on the origin of the \((E/Z)\) isomer ratio of imines in the ISM; thus they show that the less-stable \((E)\) conformer of cyanomethanimine, RCH═NH, where R is a C═N group, rearranges to the \((Z)\) conformer with dramatically increased rates over canonical transition-state theory values at temperatures of 250 K and below. The variational effect is small and the faster rates are ascribed to quantum tunneling; exactly the same as found here.

The detection of isotopically labeled compounds can be useful for tracing formation routes; specifically, deuterium has been used in this regard by Bianchi et al.,\(^{60}\) in their study of CH\(_3\)C═ND in the SVS13-A Class I hot corino. Unfortunately, such a tool is unavailable here since the hydrogen transferred has been sourced from the water–ice; however, if CH\(_3\)C(OH)ND or CH\(_3\)C(OH)NH\(_2\) were to be detected, then that might prompt other avenues of investigation.

**Intermolecular Route.** The same outcome, that is RC(OH)-NH → RC(O)NH\(_2\), can come about by the attack of hydronium at the N-atom leading similarly to R–C(OH)=NH\(_2\)+ + H\(_2\)O and attack by a further water molecule at the O-atom leading to deprotonation, resulting in the final products R–C(O)=NH\(_2\)+ + H\(_2\)O\(^{1}\).

So this reaction follows the same course mechanistically as the first; first, protonation at the nitrogen atom, which has a tiny barrier of 1.6 kJ mol\(^{-1}\) (disappears when adding ZPE), is followed by H-abstraction from the OH group and transfer of H to a neighboring water and transfer of H to a second water,

![Figure 5](image.png)

**Figure 5.** Intermolecular HC(OH)═NH → HC(O)NH\(_2\).

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the carbon–nitrogen triple bond has a much higher barrier of 220 kJ mol\(^{-1}\) so the catalytic reaction HCN + 32H\(_2\)O·H\(_2\)O\(^{+}\) → HC(OH)NH + 31H\(_2\)O·H\(_2\)O\(^{+}\) represents a considerable reduction in barrier height.

As noted in the Introduction many schemes have been proposed for the formation of amides in the ISM but none have been judged to be convincing\(^{22,26,66}\). The most often proposed are barrierless radical–radical recombination reactions such as HCO\(^{+}\) + NH\(_3\) but this suffers from a number of disadvantages in comparison to the catalytic reaction. First, the two radicals must diffuse toward each other in/on the water–ice and their rates of diffusion are considerably slower than the “diffusion” of H\(^+\) in the ice. Second, the absence of cross-products such as HC(O)–HC(O) and NH\(_2\)H\(_2\), none of which have been detected\(^{62}\) in the ISM, presents a challenge to this viewpoint. Third, the rate of reaction, \(R\), is proportional to the product of the concentrations \(R \propto [HCO^{+}] \times [NH_{3}^{*}]\), both of which are very low, whereas for the proposed catalytic reaction the concentration of water, which is the actual reactant, in the ice is considerably greater.

Since there has been very little work done previously on charged species reacting in/on water–ice grains, it might be argued that ion–molecule reactions known to occur barrierlessly in the gas-phase might be a guide to what happens in/on acidified water–ices. But this is not a reliable guide since protonation, attack by H\(_2\)O and reformation of H\(_2\)O\(^{+}\), is a concerted process according to our results; this is not the case in the gas-phase where these reactions occur in a stepwise manner. We note that KIDA, the Kinetic Database for Astrochemistry, lists many reactions leading to the formation of HCNH\(_1\); however, it does not include any reactions for HCNH\(_{1}^{+}\) + H\(_2\)O other than the reverse reaction.\(^{63}\) For these reasons, we conclude that the reaction on water–ice is a considerably more efficient process and also a mechanism that is potentially applicable to all cyanides, vide infra, not just to hydrogen and methyl cyanides.

Since the hydronium ion is such a novel reactant, in the context of amide formation in interstellar space, can it be argued that H atoms are more likely to be involved? Although we have not attempted to model such a system, HCN + 33H\(_2\)O\(^{+}\), it is known from theoretical work\(^{64}\) that HCN + H\(^{+}\) → H\(_2\)C\(_{\equiv}\)N\(^{+}\) is preferred over HCN + H\(^+\) → HCNH\(^{+}\). Further reactions with H\(^+\) will lead, most probably, to amine formation, not amide.

The presence of other species on the ice, such as, for example, methanol, carbon dioxide, or ammonia, might outcompete and negate the hydrolysis of RC\(_{\equiv}\)N but this is a topic beyond the scope of this article since modeling a system like [HCN·CH\(_3\)OH·32H\(_2\)O·H\(_2\)O\(^{+}\)] would majorly exceed our resources. In very general terms, one can surmise that the presence of ammonia on the water–ice would be expected to mop up any H\(_2\)O\(^{+}\) forming the very stable ammonium ion, NH\(_3\)\(^{+}\), leading to the cessation of any further reaction—ammonia would act as a sink for H\(_2\)O\(^{+}\). This argument is based on the very rough estimate that highly exothermic reactions tend to have lower energy barriers than very endothermic reactions, and, on the relative proton affinities\(^{65}\) of HCN and NH\(_3\), which are 713 and 854 kJ mol\(^{-1}\), respectively. Competition for H\(_2\)O\(^{+}\) between substances with a lower proton affinity, for example, CO\(_2\) at 594 kJ mol\(^{-1}\) on the other hand would favor reaction with HCN.

There are of course other nitriles present in the ISM and one would anticipate that a similar fate would befall them; Manna and Pal\(^{66}\) have detected the unfortunately named cyanamide, or amino cyanide H\(_2\)NC\(_{\equiv}\)N, in the hot molecular core G10.47 + 0.03 and outline three possible fates, degradation to H\(_3\)N\(^+\) + CN\(^-\) by cosmic rays and high-energy photons or by ion–neutral reactions: H\(_3\)NC\(_{\equiv}\)N + H\(^{+}\) → H\(_3\)NC\(_{\equiv}\)NH\(^+\) + H\(_2\).

In an extensive computational study by Slate et al.\(^{66}\) into urea formation in the ISM, they concluded that closed shell reactions had prohibitive barriers but that a route involving charged species was feasible except that their starting point involved isocyanic acid HN\(_{\equiv}\)C\(_{\equiv}\)O with protonation at the O atom followed by addition of ammonia and subsequent deprotonation; a somewhat more complex sequence than that envisaged here but nevertheless comparable. Previously Brigiano et al. had considered ion–molecule, neutral–neutral, and radical reactions leading to the formation of urea but only in the gas-phase.\(^{67}\)

Catalytic addition of water on ice-grains to cyanamide H\(_2\)N–C\(_{\equiv}\)N, which is known to exist in the ISM,\(^{68,69}\) would lead to the formation of carbonyl diamide, OC(NH\(_3\))\(_2\), better known as urea, which has been detected previously.\(^{70,71}\) In other work we have shown that the tautomerization reaction R–C(OH)NH → R–C(O)NH\(_2\) proceeds at a much faster rate in the gas-phase for R = H\(_2\)N than for any of those imidic acids with R = H\(_2\)NO\(_{\equiv}\)C\(_{\equiv}\)H\(_2\)CN\(_{\equiv}\), H\(_2\)C\(_{\equiv}\)H\(_2\)CH\(_2\)CH\(_2\)N\(_{\equiv}\)CN\(_{\equiv}\), H\(_2\)C\(_{\equiv}\)(O)\(_{\equiv}\)N\(_{\equiv}\)CH\(_2\)C\(_{\equiv}\)H\(_2\)N\(_{\equiv}\)CN\(_{\equiv}\). Urea is a key intermediate in biosynthetic pathways. and recent work outlines ways in which urea is of fundamental importance to the prebiotic chemistry that gave rise to life on our planet\(^73\).—Darwin’s “warm little pond” scenario.\(^74\)

### CONCLUSION

The catalytic addition of acidic water to RC\(_{\equiv}\)N triple bonds is shown to be a credible process on water clusters, which are impacted by hydrons H\(^+\). We refer in the paper to the very high barrier for the direct reaction HCN + H\(_2\)O in excess of 220 kJ mol\(^{-1}\) and demonstrate that the presence of catalytic amounts of H\(_2\)O\(^{+}\) dramatically reduces the barrier to reaction of 79 kJ mol\(^{-1}\) for HCN and 52 kJ mol\(^{-1}\) for CH\(_3\)CN. The high mobility of the hydron through the cluster leads to the initial reactive step, protonation at the N atom in a facile manner. This effectively transforms a bimolecular reaction into a unimolecular process—thereby removing the “collisional handicap” which hampers all gas-phase reactions in the interstellar medium.

Concerted attack by water at carbon and abstraction of H\(^+\) yields the hydroxy imine RC(OH)NH which can then undergo a 1,3\([H]\)-transfer reaction either intramolecularly or intermolecularly to the amide RC(O)NH\(_2\). Quantum-mechanical tunneling plays a key role in these processes.

The current paradigm which emphasizes radical–radical combination on grains, R\(_1\) + R\(_2\) → R\(_1\)R\(_2\) as possible formation routes for complex organic molecules because such reactions are barrierless but the absence of the cross-products R\(_1\)R\(_1\) and R\(_2\)R\(_2\) and the low probabilities of the two radicals separately arriving on said grain may need to be reconsidered in the case of the formation of amides.

The recent review by Woon with its stress on the need to pay more attention to cation reactions in ices is shown to be prescient and his call for experimental confirmation timely.

### ASSOCIATED CONTENT

**Data Availability Statement**

The data that support the findings of this study are available on request from the corresponding author.
The authors declare no competing financial interest.

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J.M.S. and B.K. contributed equally to this work.

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