Formamide reaction network in gas phase and solution via a unified theoretical approach: Toward a reconciliation of different prebiotic scenarios

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Increasing experimental and theoretical evidence points to formamide as a possible hub in the complex network of prebiotic chemical reactions leading from simple precursors like H₂, H₂O, N₂, NH₃, CO, and CO₂ to key biological molecules like proteins, nucleic acids, and sugars. We present an in-depth computational study of the formation and decomposition reaction channels of formamide by means of ab initio molecular dynamics. To this aim we introduce a new theoretical method combining the metadynamics sampling scheme with a general purpose topological formulation of collective variables able to track a wide range of different reaction mechanisms. Our approach is flexible enough to discover multiple pathways and intermediates starting from minimal insight on the systems, and it allows passing in a seamless way from reactions in gas phase to reactions in liquid phase, with the solvent active role fully taken into account. We obtain crucial new insight into the interplay of the different formamide reaction channels and into environment effects on pathways and barriers. In particular, our results indicate a similar stability of formamide and hydrogen cyanide in solution as well as their relatively facile interconversion, thus reconciling experiments and theory and, possibly, two different and competing prebiotic scenarios. Moreover, although not explicitly sought, formic acid/ammonium formate is produced as an important formamide decomposition byproduct in solution.

chemical reactions | free energy landscapes | ab initio molecular dynamics | formamide | prebiotic scenarios

Very different environments have been suggested as possible cradles for the emergence of biomolecules, including a primordial liquid soup (1), rarified gaseous interstellar clouds (2, 3), liquid–solid interfaces at hydrothermal conditions (4), and the extreme case of impact sites of meteorites and comets (5). Biochemically relevant reactions can be fueled by a range of different energy sources, and a large number of possible chemical reactions and reaction paths are suggested to have played an important role in the process leading simple molecules to form small organic molecules and, from them, biological monomers and polymers.

Among such small organic molecules, formamide is assuming an ever more central role in prebiotic chemistry research, as recently shown in experiments mimicking some of those origins of life scenarios, such as laser sparks (6), UV light (7), proton irradiation (8), or shock waves (as in meteorite impacts) (9). The main reason for such strong interest in formamide, besides its ubiquitousness in the solar system, is its chemical flexibility: it can be formed from (or, conversely, dissociated into) different molecular species that represent fundamental building blocks, including H₂, H₂O, NH₃, CO, HCN, HNCO, and HCOOH (10, 11). The barriers for these different processes lie in a relatively narrow range, providing many synthetic directions. Additionally, as has been also showed experimentally and computationally, formamide could give rise to all classes of biomolecular monomers, from amino acids to nucleic acids to sugars (12, 13).

For example, inspired by the classic Miller experiments, recent ab initio MD (AIMD) simulations demonstrated that an intense

electric field can induce the barrierless (spontaneous) formation of formamide and formic acid from a CH₄, CO, NH₃, H₂O, and N₂ mixture in the condensed phase, and under the same conditions, formamide in turn gives birth to more complex organic molecules including glycine (14). In this context, understanding the thermodynamics (free energy differences) and kinetics implied in basic reactions of prebiotic relevance is key to assess the likelihood of the different scenarios put forward in the literature. Computational approaches are a formidable complement to experiments in this field because they exploit the fundamental laws of quantum mechanics to study chemical reactions, interpret experimental results, and predict novel mechanisms.

However, contemporary computational physical chemistry is dominated by gas-phase calculations at zero temperature, with effects due to temperature, pressure, and chemical environment relegated to approximated extrapolations. For instance, our knowledge of reaction dynamics in condensed phases is far from complete (15, 16), despite the fact that water is a polyvalent molecule, known to participate also in formamide chemistry under different roles, including as a stabilizer through hydrogen bonds, as an efficient acid–base bifunctional catalyst, and as a coreactant (17). Additional effects should also be considered, including vibrational energy dissipation upon birth of exothermic products or solute trapping into finite-lifetime cages affecting its diffusion and reactivity (16, 18, 19). The large number of possible configurations [already including few water molecules (17)] together with the strong anharmonicity of liquids naturally calls for methods like MD that include from the start the finite-temperature dynamics.

Significance

The qualitative and quantitative description of chemical reactions is a formidable problem. Determining pathways, energetics, and kinetics requires costly accurate quantum approaches. Typically, this amounts to a simplification of gas-phase reactions into elementary steps, which, in turn, are usually directly translated in solution. The topology-based method hereby presented allows instead an unbiased exploration of both gas-phase and aqueous-phase reactions. Its application to formamide, a centerpiece of prebiotic chemistry, unveils very different reaction networks between gas and solution regimes, indicating, in the liquid phase, new pathways, intermediates, and products. The new scheme allows us also to demonstrate the comparable relative stability of formamide, hydrogen cyanide, and formic acid, thus contributing insight to a heated current debate in the prebiotic chemistry community.

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Fig. 3. Free energy landscape for reactions in aqueous solution between formamide (region A), CO + NH₃ (region B), and HCOOH + NH₃ (region C). Representative atomic configurations are shown as insets.

Results

Decomposition of Formamide into Carbon Monoxide and Ammonia.

In a first set of simulations we investigated decarbonylation reactions and their inverse:

Within a single gas-phase simulation of 170 ps the trajectory explores seven forward and seven backward reactions. In the resulting free energy landscape (Fig. 2) two basins corresponding to reactants and products are readily identified, differing by less than 1 kcal/mol in stability. Reactants and products are separated by a free energy barrier $\Delta F^* = 79$ kcal/mol, very similar to the barrier of 80.5 kcal/mol found in zero-temperature calculations at CCSD(T)/CBS + ZPE level in ref. 10.

Compared with gas phase, the landscape of the solution is significantly modified in both quantitative and qualitative features (Fig. 3). In particular, besides the reference states used to build the collective variables (formamide and $\text{CO} + \text{NH}_3$), the simulation explores a third basin featuring formic acid plus ammonia. This finding is remarkable because our space of collective variables was not explicitly constructed to take into account formic acid, as shown from the higher values of the z coordinate with respect to the reference species. Formamide, $\text{CO} + \text{NH}_3$, and $\text{HCOOH} + \text{NH}_3$ show a similar stability within our statistical uncertainty (± 2 kcal/mol). Inspection of the landscape results also in a barrier of 35 kcal/mol for the reaction $\text{HCONH}_2 \rightarrow \text{HCOOH} + \text{NH}_3$ and of 40 kcal/mol for the reaction $\text{HCONH}_2 \rightarrow \text{CO} + \text{NH}_3$. For comparison, repeating the simulation in the larger cell containing 62 water molecules (see values in parentheses in Table 1), we found differences in the free energy levels corresponding to minima and saddle points that are within 5 kcal/mol from the smaller model ones.

The two decomposition channels, decarbonylation and hydrolysis, thus have quite similar barriers, confirming the effectiveness of topological path collective variables in discovering competitive pathways and even relevant chemical species. Additionally, ionic forms NH_4^+ and HCOO^- are also explored, as expected from the basicity of ammonia and acidity of formic acid. An advantage of our molecular dynamics approach is to have built-in anharmonic temperature effects, so that we can directly break down ΔF into energetic and entropic contributions: ΔE is directly obtained as the average energy observed in a relatively long equilibrium (unbiased) MD simulation performed in each metastable state (*Supporting Information*), whereas $T\Delta S = \Delta E - \Delta F$. As shown in Table 1, energy differences among the three product states are

small, whereas all decomposition reactions correspond to a sizable increase in energy that is almost exactly compensated by an increase in entropy, resulting in a comparable free energy for all four metastable states. As detailed in [Supporting Information](#), the different solute molecules interact in very different ways with water: formamide and formic acid are highly hydrophilic engaging on average in 4.5 and 5 hydrogen bonds with water, respectively, within an equilibrium MD simulation. Instead, CO appears as a hydrophobic molecule, not engaging in hydrogen bonds and featuring a first solvation shell at the sizable distance of 3.5 Å, similar to the hydrophobic cage of water molecules observed around solvated CO₂ (19).

In more detail, all observed reactions begin with water donating a proton to the amino group of formamide as the first step (leaving an OH^- species in solution), overcoming a barrier $\Delta F^\ddagger \approx 35$ kcal/mol. The resulting cation, which was identified as a relevant intermediate for this same reaction in ref. 14, is locally stable only within a time scale of less than 1 ps, as we verified with hundreds of unbiased trajectories started from 10 different configurations featuring this species (see committor analysis below). Experimentally, formamide is a weak base, with the protonated species having a standard free energy almost equivalent (only 0.1 kcal/mol higher) to the neutral species (39); however, the carbonyl is expected to be the most probable protonation site (40), in agreement with the transient nature of the protonated nitrogen in our simulations. Due to the transient nature and very short lifetime of the HCONH_3^+ intermediate, the mechanism could also be approximately considered as one step. From HCONH_3^+ the system can evolve either toward carbon monoxide and ammonia or toward formic acid and ammonia: we focus here on the former channel and discuss the latter in next section. The dissociation of the C–N bond is accompanied by the donation of the carbon-bound proton to water. The mechanism appears fully reversible in our simulations, with backward transitions (formamide formation) featuring a barrier of 40 kcal/mol. The barrier can be flattened by a strong enough electric field as demonstrated in ref. 14. We validated the mechanism and assigned transition state structures by performing a committor analysis, as detailed in [Supporting Information](#). We could then identify the transition state structures as those giving approximately 50% probability to fall in either basin, as shown in Fig. 4. Note how both steps of the reaction, nitrogen protonation and carbon deprotonation, are enabled by the solvent, whereas in our gas-phase simulations the very same proton was transferred from the carbon to the nitrogen overcoming a higher barrier. We also remark the striking difference between committor trajectories in solution (Fig. 4), wandering in the low-curvature landscape regions for more than about 100 fs, compared with those in gas phase ([Supporting Information](#)) resembling steepest descent relaxation pathways due to the lack of solvent collisions.

We could not observe direct transitions between the basins corresponding to $\text{CO} + \text{NH}_3$ and $\text{HCOOH} + \text{NH}_3$; transitions pass instead close to the formamide basin, pointing to a catalytic role of ammonia in the conversion process between CO and HCOOH. Our result reinforces the important role of ammonia in prebiotic chemistry from multiple points of view, including as a reactant

Table 1. Energetic differences (kcal/mol) of the main states in aqueous solution at $T = 300$ K, with formamide taken as a reference

State	ΔF	ΔE	$-T\Delta S$
HCONH ₂	0 (0)	0	0
CO + NH ₃	-5 (-3)	21	-26
HCOOH + NH ₃	0 (-5)	20	-20
HCN + H ₂ O	1 (-4)	18	-17

Models include 30 water molecules (62 in parentheses).

Fig. 4. Examples of unbiased trajectories observed within committor analysis and representative structures of transition states for reactions among formamide, $\text{CO} + \text{NH}_3$, and $\text{HCOOH} + \text{NH}_3$.

for the synthesis of formamide, as a catalyst for formic acid synthesis, and as pointed out in a recent experimental study as an essential ingredient for the formation of sugar-related aldehydes from UV-irradiated water and methanol ice mixtures mimicking protostellar clouds (41).

Hydrolysis of Formamide into Formic Acid and Ammonia. We proceed to study hydrolysis reactions and their inverse:

This reaction channel emerged (even if it was not explicitly sought) as a formamide decomposition pathway alternative to decarbonylation in our previous liquid-phase simulation. Due to the key role of water molecules as (at least) a coreactant, we uniquely addressed the liquid-phase processes. Experimentally, at pH-neutral conditions the hydrolysis has a pseudo-first-order rate of $3.6 \cdot 10^{-9} \text{ s}^{-1}$ at 56°C (42); however, the mechanism and free energy profile of the process have not been compellingly assigned. Based on static calculations including five water molecules, ref. 43 claimed that hydrolysis would proceed preferentially through a water-assisted two-step mechanism, with the formation of an amino-gem-diol intermediate $\text{CH}(\text{OH})_2\text{NH}_2$ (by adding water to the CO bond, the rate limiting step) followed by proton transfer from one OH group to the nitrogen and simultaneous dissociation of the CN bond. Previous Car-Parrinello steered-MD simulations of the aqueous solution (44), based on the C–O distance as reaction coordinate, suggested instead a concerted one-step mechanism with direct addition of water to the carbon in a tetrahedral transition state. Theoretical and experimental results were also interpreted in terms of a zwitterion mechanism. We also recall that the Miller-like *ab initio* simulations in ref. 14 identified formic acid as an important prebiotic intermediate species, together with formamide, on a pathway toward the synthesis of glycine facilitated by an external electric field.

In our simulations the hydrolysis of formamide preferentially follows a two-step mechanism: First, the nitrogen is protonated, forming the transient HCONH_3^+ cation with a barrier of $\Delta F^\ddagger \approx 35$ kcal/mol (as discussed in the previous section). Inspection of the multiple reactive trajectories observed with metadynamics suggests that OH^- addition to the carbon leads to the dissociation of the C–N bond, thus completing the two-step reaction (albeit a quite unstable intermediate). The backward reaction is also observed simply reverting the steps. Our barrier of 35 kcal/mol is similar to the one of ref. 43 and, as shown therein, is in agreement with the available kinetic experimental data (42);

however, we remark how our two-step mechanism is different from the one proposed from the calculations in ref. 43 because it does not pass through an amino-gem-diol intermediate (that we sporadically also observe off-pathway). The different result in ref. 43 could be related to the simplified model of solution (including five water molecules) used by the authors. On the other hand, they adopted a theoretical approach for the quantum mechanical treatment of electrons, which is generally more accurate than the DFT approach used in the present work. The one-step mechanism proposed from Car-Parrinello simulations in ref. 44 is also unlikely because it features a higher barrier (45 kcal/mol), possibly due to the simple collective variable used by the authors, the C–O distance, that includes far fewer degrees of freedom than our topological path collective variables. Note that in ref. 45, metadynamics made it possible to explain the experimental barrier [21 kcal/mol (42)] for base-catalyzed hydrolysis, namely, OH[−] attack without prior protonation of the nitrogen. We validated the metadynamics scenario with a committor analysis, resulting in the transition state structures displayed in Fig. 4.

Reactions Connecting Formamide with Hydrogen (Iso)cyanide. We finally address the following reaction:

In gas phase, similar to before, we initially defined path collective variables based on the coordination patterns of formamide (reference state 1) and $\text{HCN} + \text{H}_2\text{O}$ (reference state 2). However, whereas for decarbonylation we observed trajectories interconverting reactants and products without passing through intermediates, here the simulations revealed a more complex scenario. All reactions begin by the isomerization of formamide into OHCHNH through direct hydrogen transfer from nitrogen to oxygen. Next, the isomer evolves toward $\text{HNC} + \text{H}_2\text{O}$, it reverts to a different OHCHNH isomer, and only at this point it reacts to form $\text{HCN} + \text{H}_2\text{O}$: The main barriers are 45 kcal/mol for the initial internal proton transfer and 55 kcal/mol for the final dissociation giving HCN and water [to be compared with barriers of 42 and 59 kcal/mol, respectively, from zero temperature calculations at $\text{CCSD(T)} + \text{ZPE}$ level (10) and similarly at B3LYP level (46)]. The gas-phase scenario is of limited interest here (except for comparison with previous zero-temperature calculations): its detailed analysis is in [Supporting Information](#). In solution the interconversion between formamide and HCN is still a multistep process (Fig. 5). The first step consists again of the formation of OHCHNH , however, with the nitrogen-to-oxygen hydrogen transfer occurring

Fig. 5. Free energy landscape for reactions in aqueous solution between formamide (region A), OHCHNH (region B), and HCN (region C). Representative atomic configurations are shown as insets.

Fig. 6. Examples of unbiased trajectories observed within committor analysis and representative structures of transition states for reactions between OHCHNH and HCN. The orange contour indicates atoms belonging to the reacting OHCHNH molecule.

through a proton chain in the solvent, sizably reducing the barrier to only 25 kcal/mol. Next, we observed a number of facile interconversions between the four different OHCHNH isomers, again thanks to proton exchanges with the solvent rather than dihedral rotations (which, however, are also present). HCN is then obtained overcoming a barrier of about 20 kcal/mol (or 45 kcal/mol taking formamide as a reference), the reverse barrier being about 44 kcal/mol. For comparison, barrier heights computed in gas-phase clusters including three or four water molecules at zero temperature and CCSD(T) + ZPE level are 21 kcal/mol from formamide to OHCHNH, similar to our value of 25 kcal/mol, and 35 kcal/mol from OHCHNH to HCN, sizably larger than our value of 20 kcal/mol; additionally, HCN is destabilized by 14 kcal/mol with respect to our results (or by 19 kcal/mol considering our larger 62-waters simulation box) (17). These findings show the importance of realistic models of solutions and of the fully anharmonic dynamics at finite temperature. According to committor analysis, the crucial reaction step is a proton transfer from the NH moiety to a water molecule, followed by the dissociation of the OH unit of the isomer and its protonation by the solvent to generate a water molecule (Fig. 6). The process occurs through a hexagonal ring with the participation of three water molecules plus the newly generated one.

The free energy difference between formamide and HCN (plus water) is small—as confirmed also using a larger 62-waters model (Table 1)—thanks to the favorable entropic term canceling out the unfavorable energetic one. The relative stability emerging from our simulations is in reasonable agreement with an experiments-based model of primitive oceans giving, at pH = 7, a free energy difference of only 4 kcal/mol (47). This fact may be interpreted in the sense of both molecules having been largely available, given appropriate conditions, for possible prebiotic processes.

HCN appears as weakly hydrophilic, engaging on average in 0.5 hydrogen bonds with water and featuring a first solvation shell of radius 2.3 Å. Occasionally, overcoming a small barrier, HCN is also deprotonated to cyanide ion, at higher values of the z -path coordinate. At variance with the gas phase, in solution, HNC is not locally stable, occasionally forming but then immediately disappearing within a time scale of ~ 0.1 ps. This observation is consistent with HNC being mainly found in interstellar clouds (48) and only in gas-phase laboratory experiments (49), and it could be interpreted in terms of HNC having a much more acidic proton than HCN.

An interesting question is how temperature and pressure modify prebiotic reaction networks, because different scenarios are characterized by different boundary conditions. As a first step in this direction we repeated gas-phase and liquid solution simulations at $T = 400$ K, keeping identical collective variables and simulation setup. The corresponding reaction landscapes (reported in *Supporting Information*) show that in gas phase the effect on free energy differences is limited to within 3 kcal/mol, thus compatible with our statistical error bar of ± 2 kcal/mol, whereas in solution both the transition state between OHCHNH and HCN and the local minimum of HCN are destabilized by 10 kcal/mol in passing from 300 to 400 K. The destabilization of HCN compared with formamide is traced back to an increase in ΔE (from 18 to 25 kcal/mol) concomitant with a decrease in ΔS [from 57 to 38 cal/(mol K)]. The latter variation is consistent with an increased freedom of the formamide molecule and decreased freedom of HCN: the average number of solute–solvent hydrogen bonds passes from 4.5 to 3.6 for formamide and from 0.5 to 0.9 for HCN. The sizable deviation from a temperature extrapolation at rigid ΔE and ΔS strongly supports the usefulness of our approach and, more generally, of MD simulations.

Conclusions

In conclusion, we have developed a novel approach which allows the study of chemical reactivity in gas phase and in liquid phase on the same footing, through the definition of simple, intuitive, and transferable reaction coordinates. In combination with state-of-the-art free energy calculation methods such as metadynamics, the new coordinates allow us to discover relevant reaction mechanisms and reconstruct the corresponding free energy landscapes, which can be directly compared between phases and/or at different thermodynamical conditions. Finally, detailed inspection of trajectories and committor analysis allow us to compellingly identify transition states and reaction pathways and mechanisms.

We apply this new approach to the emblematic case of formamide, a centerpiece of many prebiotic scenarios recently put forward to explain the chemical origins of life on Earth. On one hand, our method is capable of quantitatively reproducing existing gas-phase results. Much more importantly, liquid-phase calculations—for which our approach is a major methodological step forward—of all three fundamental reaction channels, i.e., dehydration, decarbonylation, and hydrolysis, provide novel results of prebiotic significance and implications. In fact, previous gas-phase studies (even including few water molecules) suggested formamide as thermodynamically much more stable than hydrogen cyanide, a fundamental prebiotic molecule and a precursor in crucial biochemical syntheses. Within the approximations of this work, namely, the DFT level treatment of the electronic problem and the classical treatment of protons, we show that formamide and hydrogen cyanide in explicit solution have instead a comparable stability and relatively facile interconversion, as pointed out experimentally by Miller and coworkers (47). Our results thus suggest the formamide-based and the hydrogen cyanide-based prebiotic scenarios to be compatible, contributing to settle a recent high-pitched debate on the question. Finally, our uninformed reaction network exploration unveils ammonium formate as a major species in formamide decarbonylation/hydrolysis, of comparable stability with respect to both formamide and hydrogen cyanide, and thus supporting its major role among fundamental prebiotic actors.

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