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Influence of Inlet Capillary Temperature on the Microdroplet Chemistry Studied by Mass Spectrometry

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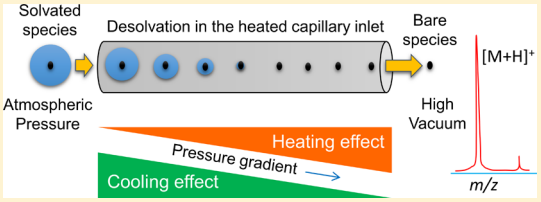
Supporting Information

ABSTRACT: Often, studies of microdroplet chemistry using electrospray ionization mass spectrometry (MS) either find a negligible effect of the heated inlet capillary of the mass spectrometer on the reaction rate or do not consider its effect. In this context, we studied two reactions in microdroplets, the Pomeranz−Fritsch synthesis of isoquinoline and the Combes quinoline synthesis. The reagents were electrosprayed with methanol and aqueous solutions forming small and large microdroplets at flow rates of 1 and 20 μL/min, respectively. We also varied the inlet capillary temperature from 100 to 350 °C. Contrary to the view that the inlet temperature has little to no influence on the reaction rate, we found that the Pomeranz−Fritsch reaction was markedly accelerated for both solvents and for both droplet sizes on increasing the temperature, whereas the Combes synthesis showed the opposite behavior. We propose that these strikingly different behaviors result from a competition of two effects, the evaporative cooling versus the heating of ejected bare ions from the droplet, both taking place inside the heated inlet. This finding suggests that these phenomena must be taken into account while interpreting the microdroplet reactions studied by electrospray or a similar kind of ambient ionization MS.



INTRODUCTION

Microdroplet chemistry is a newly emerging field with potential applications in accelerating the rates of chemical reactions, chemical synthesis, and studying reaction kinetics and mechanisms.[1−7] Particularly, in the last few years, several reports by others and our group have substantiated the usefulness of microdroplets in speeding up chemical transformation by many orders of magnitude when compared to the corresponding conventional bulk-phase reaction.[2,3,6,8−21]

Several factors such as pH, surface charge, reagent confinement, desolvation, droplet size, solvent composition, air−liquid interface, contact ion pairing, temperature, large electrostatic pressure, and molecular orientation on the droplet surface can collectively affect the microdroplet to become a powerful microreactor.[10] Many analytical studies on microdroplet chemistry have employed electrospray ionization mass spectrometry (ESI-MS) for online detection of the reactants, intermediates, and products. Figure 1 depicts a microdroplet reaction study using ESI-MS,[22−24] where the reactant solution is delivered by a coaxial sheath gas (nitrogen) flow to the tip of an electrospray source held at a high potential with respect to the inlet of the mass spectrometer. This causes the spraying of charged aerosol in the air. Solvent electrolysis accumulates charges (e.g., protons in the positive ion mode) at the surface of the droplet.[22,25] When the electrostatic force exceeds the surface tension of the liquid, droplets disintegrate by Coulomb explosion.[22,26] Often the spray source is surrounded by a gas flow of higher pressure, typically, dry N_2, which helps in the evaporation of droplets to some extent and propel them toward the mass spectrometer inlet.[27] Typically, the inlet of the mass spectrometer is kept at a high temperature to complete desolvation and the droplet evolution process forming ions in vacuum for their detection.[26] It is thought that droplet fission occurs repeatedly until bare ions or small clusters of ions surrounded by solvent molecules enter the mass spectrometer.[26,28]

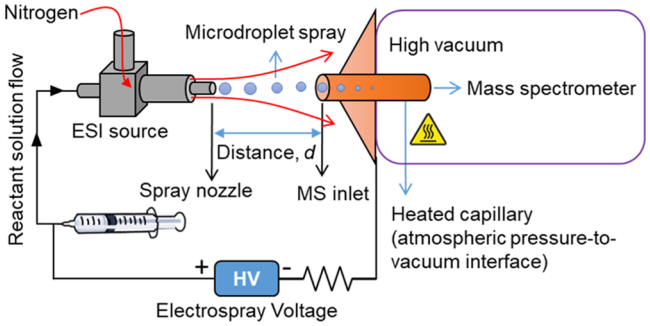


Figure 1. Schematic diagram of the experimental setup for studying microdroplet chemistry using ESI-MS.

In studying microdroplet reaction kinetics,[1,2,8,16,29,30] the reaction time (droplet lifetime; in the order of a millisecond[22,26]) is varied by changing the distance d (Figure 1) between the spraying nozzle and the inlet of the heated capillary followed by the detection of reactants and/or

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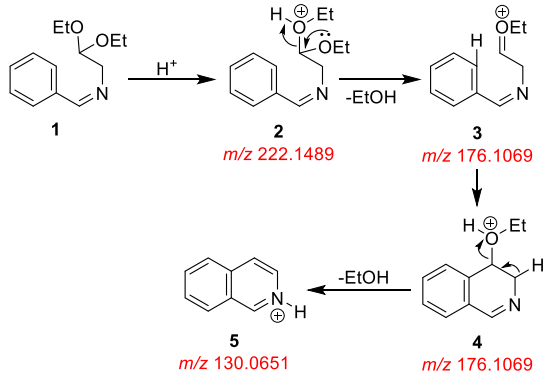
products by MS.[8,11,16,30] This method assumes that the reaction is stopped when the droplet enters the heated inlet of the mass spectrometer.[11,30] Supportive evidence has also been presented by us earlier on considering this assumption for estimating the kinetics in microdroplets of acid-induced unfolding of cytochrome *c* and hydrogen−deuterium exchange in bradykinin.[2] The possible reason for ceasing the microdroplet reaction in the heated capillary region can be attributed to rapid evaporative cooling and a sudden conversion of the solvated ions into free gaseous ions.[26] Indeed, a recent report showed that the rapidly evaporating water microdroplet can reach a supercool state with a temperature as low as −42 °C.[31] Thus, it is not surprising that such a low temperature can slow down the microdroplet reaction followed by complete desolvation of species from the reaction. A recent report by us on epoxide ring opening in microdroplets showed no variation in the product yield upon changing the inlet capillary temperature.[14] This observation confirms the rapid quenching of the microdroplet reaction in the heated capillary region, which is in line with our earlier reports also.[2] This effect of temperature of the heated inlet capillary on the microdroplet reaction studied by MS is not sufficiently noted in the literature. However, this study appears to be crucial in supporting the contention that the heated capillary zone has negligible or no effect on the microdroplet reaction kinetics studied by MS. In this regard, we have investigated two reactions, for example, Pomeranz−Fritsch synthesis of isoquinoline (Scheme 1) and Combes quinoline synthesis

Scheme 1. Plausible Mechanism of the Acid-Catalyzed Pomeranz−Fritsch Synthesis of Isoquinoline 5 Starting from the Benzalaminoacetal 1 in Microdroplet[a]



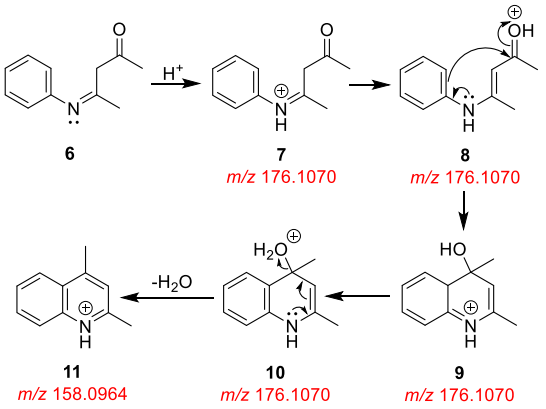
[a]The theoretical *m*/*z* values of all ionic species are given in red color below their structures.

(Scheme 2), which we previously reported showing their remarkable reaction rate acceleration (>10^6 for the former and >10^3 for the latter) in the microdroplets.[3] Variation in the droplet size and charge on the droplet strongly contributed to the reaction rate indicating the effect of charged microdroplet environment on those reactions. The present study on the above two reactions reveals here how the measurement of the reaction rate acceleration caused by microdroplets can be affected by the heated inlet of the mass spectrometer.

EXPERIMENTAL SECTION

Chemicals were purchased from Sigma-Aldrich (St. Louis, MO). High-performance liquid chromatography−MS grade solvents were purchased from Fisher Scientific (Nepean, ON,

Scheme 2. Plausible Mechanism of the Acid-Catalyzed Combes Synthesis of Quinoline 11 Starting from 4-(Phenylimino)-2-pentanone 6 in Microdroplet[a]



[a]The theoretical *m*/*z* values of all ionic species are given in red color below their structures.

Canada). Synthesis of benzalaminoacetal (**1**) and 4-(phenylimino)-2-pentanone (**6**) were performed following our earlier report.[3]

Methanolic or aqueous solutions of the above analytes (0.05 mM) were electrosprayed using a home-built ESI source in the positive ion mode (+5 kV) at two different flow rates (1 and 20 μL/min) through a fused silica capillary (Polymicro Technologies, 100 μm i.d.) with a coaxial sheath gas flow of nitrogen at 120 psi. The mass spectrometer inlet capillary temperature was maintained at approximately 275 °C unless otherwise stated, and the capillary voltage was kept at 44 V. The on-axis spray distance from the spray tip to the entrance of the heated capillary was set to 1.5 cm. All experiments were carried out under identical conditions unless otherwise stated, to detect reactants and products by using a high-resolution mass spectrometer (Thermo Scientific LTQ Orbitrap XL hybrid ion trap-Orbitrap mass spectrometer). Effects of the heated ion transfer capillary (stainless steel, 4 in. length and 550 μm i.d.) on the reaction rate were studied by varying the capillary temperature from 100 to 350 °C.

Helium was used as the collision gas in the collision-induced dissociation (CID) study. CID spectra (MS^2) were acquired using an isolation width of 0.9 *m*/*z* units. The activation Q (as labeled by Thermo Scientific, used to adjust the q_z value[32] for the precursor ion) was set to 0.25, and the activation time employed was 30 ms. The normalized collision energy (NCE)[33] was varied from 0 to 60% for the dissociation profile (breakdown) study of the mass-selected ion. Data acquisition was performed for 1 min using Xcalibur software (Thermo Fisher Scientific).

RESULTS AND DISCUSSION

Following our earlier report,[3] we prepared the benzalaminoacetal **1**, which was electrosprayed in the positive ion mode to perform the Pomeranz−Fritsch synthesis of isoquinoline in microdroplets (Scheme 1) followed by monitoring the product formation using MS (Figure 1). Given the typical droplet lifetime is on the order of milliseconds,[22,26] the above reaction occurred very fast in microdroplets as evidenced by the ion signal of the protonated isoquinoline product **5** at *m*/*z* 130.0646, which is in good agreement with the theoretical value (Scheme 1). The mass spectrum for this microdroplet

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reaction[3,34] is presented in Figure S1a in the Supporting Information. Although the estimated reaction rate acceleration for this reaction was roughly found to be more than a factor of 10^6 when compared to the corresponding bulk-phase counterpart,[3] we decided to evaluate the effect of the heated capillary inlet (Figure 1) on this reaction rate. This study will help us understand the microdroplet chemistry more deeply by ascertaining the possible effect of heat on the rapidly evaporating microdroplets in driving the reaction and measuring its kinetics. Although several earlier reports have shown that microdroplet reactions stopped upon entering the heated inlet for rapid evaporative cooling,[2,11,14,16,29,30] we observed anomalous behavior of this reaction when the inlet capillary temperature was gradually increased from 100 to 350 °C.

Figure 2 shows the effects of inlet capillary temperature on the intensity ratio of the protonated product **5** (observed m/z 130.0646) to the reactant **1** (observed m/z 222.1482) for the Pomeranz–Fritsch synthesis of isoquinoline in microdroplets (Scheme 1). Two different spray solvents, methanol (Figure 2a) and water (Figure 2b), were used for this reaction at 1 and 20 μL/min flow rates, respectively. We observed a gradual increase of the reaction rate, as indicated by the product to reactant signal intensity ratio, from 100 to 275 °C inlet capillary temperature, after which a steep increment in the reaction rate was observed. The reaction occurred with almost equal effectiveness at 100 °C capillary temperature under both solvents and flow rates. However, at a low flow rate of 1 μL/min, which leads to smaller droplets, the efficiency of product formation was enhanced at higher temperatures (Figure 2). This is particularly more prominent with rapidly evaporating methanol droplets produced at a low flow rate (1 μL/min) showing nearly 23 times increment of reactivity (enhanced efficiency of product formation) on changing the inlet capillary temperature from 100 to 350 °C. Furthermore, the effect of capillary temperature on this reaction was nearly identical at a high flow rate (20 μL/min) for both solvents. At a low flow rate, the reaction from methanol microdroplets showed nearly

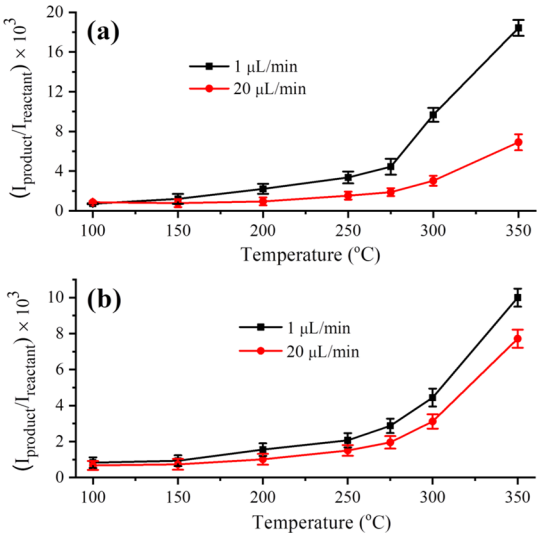

Figure 2. The extent of Pomeranz–Fritsch syntheses of isoquinoline (Scheme 1) from charged microdroplets of (a) methanol and (b) water, generated by electrospraying at 1 and 20 μL/min solution flow rates, were monitored at different temperatures of the inlet capillary.

two times higher reactivity than that observed from water microdroplets (Figure 2). The above results indicated that the reaction was further accelerated by the heat of the inlet capillary despite the effect of evaporative cooling. However, droplet evaporation assisted by both temperature and volatility of the solvent in the heated capillary inlet certainly plays a major role in controlling the droplet size and production of bare ions, which should affect the overall reaction rate.

Likewise, we also performed the microdroplet-assisted synthesis of quinoline following the Combes reaction and monitored the reaction efficiency using MS. Initially, we prepared the precursor Schiff base **6** (Scheme 2) by the condensation of aniline and acetylacetone. Following our earlier report,[3] we conducted the microdroplet reaction by electrospraying **6** in the positive ion mode. Progress of the reaction on the millisecond timescale was monitored by the ion signal of the protonated quinoline product **11** at m/z 158.0933, which is in good agreement with the theoretical value (Scheme 2). The mass spectrum for this microdroplet reaction is presented in Figure S1b, which showed an estimated reaction rate acceleration by a factor of nearly 10^3 when compared to the corresponding bulk-phase counterpart.[3]

Figure 3 shows the effects of inlet capillary temperature on the normalized intensity of the protonated product **11** for the

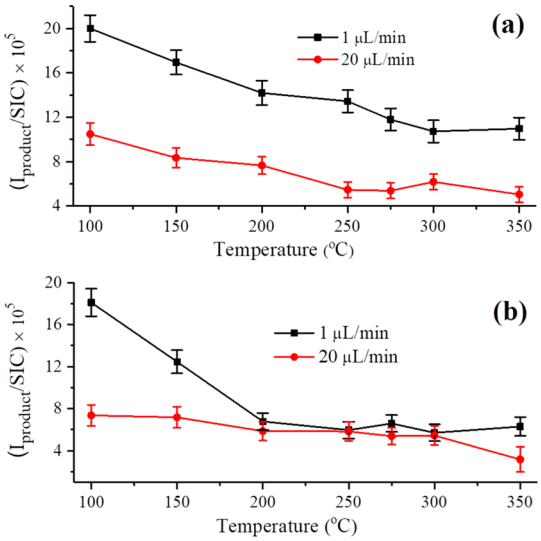

Figure 3. The extent of Combes quinoline synthesis (Scheme 2) from charged microdroplets of (a) methanol and (b) water, generated by electrospraying at 1 and 20 μL/min solution flow rates, were monitored at different temperatures of the inlet capillary.

Combes quinoline synthesis in microdroplets. As all intermediates of this reaction are isomeric with the protonated substrate **6** (Scheme 2) and we also detected several sodiated/potassiated ion signals of reactants, progress of the reaction was measured by the ratio of the ion current of the protonated product peak ($I_{product}$) and the sum of the ion currents of reactants and the product peaks (Figure S1b). In contrast to the Pomeranz–Fritsch reaction (Figure 2), the reaction efficiency for this Combes quinoline synthesis (Figure 3) gradually decreased on increasing the inlet capillary temperature from 100 to 350 °C (Figure 3). This decrease was found to be almost double at both low (1 μL/min) and high (20 μL/min) flow rates of the methanolic solution on increasing the temperature from 100 to 350 °C (Figure 3a). However, the

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reaction efficiency from the lower flow rate (smaller microdroplets) was always found to be higher than that from the higher flow (larger microdroplets) rate in the above temperature range (Figure 3a). The reaction from water microdroplets also showed similar behavior (Figure 3b), but the effect of the inlet capillary temperature on the smaller microdroplets (1 μL/min flow rate) was more prominent than that from the larger microdroplets (20 μL/min). The reaction from smaller aqueous microdroplets was not affected much above 200 °C capillary temperature although the same reaction from larger aqueous microdroplets was affected prominently beyond the temperature 300 °C (Figure 3b). Overall, the above study indicated that this microdroplet reaction is decelerated by the action of the heat of the inlet capillary.

The above two results are strikingly different from several earlier assumptions and observations that the reaction in microdroplets stopped upon entering the heated inlet for rapid evaporative cooling and ion ejection. Although it is experimentally challenging to follow what happens to a reaction, particularly in the heated capillary inlet (atmospheric pressure-to-vacuum interface), we attempt here to provide some insights into the fate of the above microdroplet reactions in this region in order to explain the different behaviors presented in Figures 2 and 3.

Our earlier work showed that both Pomeranz–Fritsch synthesis of isoquinoline (Scheme 1) and Combes quinoline synthesis (Scheme 2) could also be conducted in the gas phase by CID of the precursor protonated species (**1** or **6**), and these gaseous reactions parallel the reaction behavior (Schemes 1 and 2) observed in microdroplets and bulk solutions.[34] We performed CID on both precursor species (**1** and **6**) at different collision energies to conduct the reaction in the gas phase, and results are presented as breakdown curves in Figure 4. The CID fragmentation data showed ion signals of species corresponding to intermediates and products, m/z accuracy of

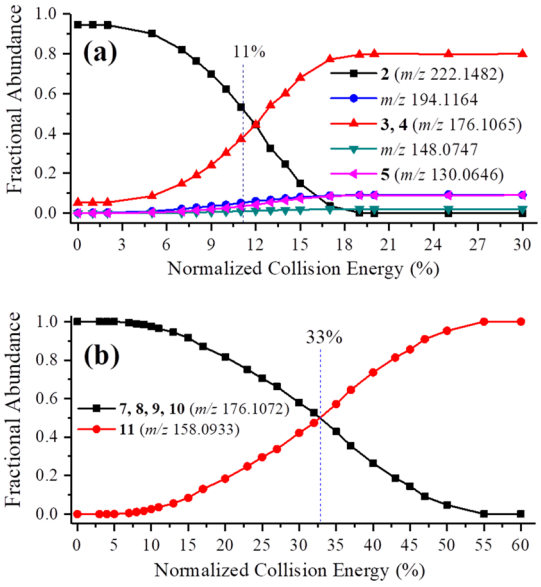

Figure 4. The CID breakdown curves[34] for (a) **2** (observed m/z 222.1482), which produces the product **5** (observed m/z 130.0646) via different intermediates in MS^2, and (b) **7** (observed m/z 176.1072), which produces species **8**–**11** in MS^2. Species **7**–**10** are isomeric and cannot be distinguished by their m/z values.

which were in good agreement with the theoretically calculated values given in Schemes 1 and 2. Some ion signals (e.g., m/z 194.1164 and 148.0747) with low abundances in Figure 4 correspond to the minor contribution of additional reaction routes found in the Pomeranz–Fritsch synthesis of isoquinoline in the gas phase.[34] Nevertheless, the CID breakdown curves provide an insight into the relative stability of the precursor species (**1** or **6**) in the gas phase albeit the derivation of the actual activation energy from the CID data is difficult and challenging because of the involvement of multiple steps and isomeric species in the reaction. The 50% breakdown of **1** in the gas-phase Pomeranz–Fritsch synthesis of isoquinoline required 11% NCE, whereas the same for **6** in the gas-phase Combes quinoline synthesis required higher energy such as ~33% NCE. These data clearly indicate that the reaction efficiency of **1** is higher than that of **6** upon collisional activation. Furthermore, this fact reconciles well with our observations that increased temperature of the inlet capillary accelerated the rate of the Pomeranz–Fritsch synthesis of isoquinoline from the protonated **1** and decelerated the rate of Combes quinoline synthesis from protonated **6**.

To explain the data more clearly, we can conceive that the heated capillary inlet acts as a cooling zone for microdroplets and a heating zone for transmitted ions. Figure 5 illustrates a

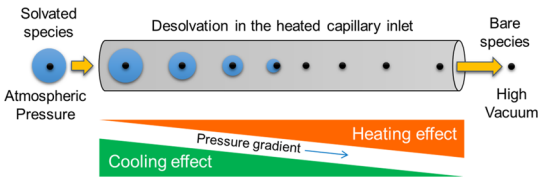

Figure 5. Competing effects of heating and cooling on the species in microdroplets and in the gas-phase in the heated capillary inlet of the mass spectrometer.

simplified process for microdroplet evolution in the heated inlet capillary, which can affect the reaction by both heating and cooling effects. The reactants encapsulated in droplets experience a cooling effect from rapid solvent evaporation as the microdroplet travels along the heated capillary. However, once the reactants and intermediates are ejected from the droplets, they are exposed to the heat of the capillary, either directly or indirectly through the density gradient of the gases inside the capillary. This causes heating of the ions as they travel along the capillary. Thus, it is expected that the capillary heat can affect the bare reactant/intermediate species causing their transformation provided the absorbed heat could achieve the activation energy barrier required for the reaction to occur. Therefore, the reaction process can be affected by both cooling and heating effects inside the capillary inlet.

The most probable reason why the increased temperature of the inlet capillary accelerated the Pomeranz–Fritsch reaction (Scheme 1, Figure 2) can be attributed to more of a heating effect than a cooling effect as explained above, which is related to the observed low energy requirement of the reaction in the gas phase (Figure 4a). On the contrary, the reaction rate deceleration of the Combes reaction (Scheme 2, Figure 3) caused by the increased temperature of the inlet capillary might be due to more of a cooling effect than a heating effect, which is related to the requirement of higher energy for the reaction in the gas phase (Figure 4b). This cooling effect imparted by the microdroplets slows down the reaction inside

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it, whereas the heating effect does not either outweigh the cooling effect or cannot cause the Combes reaction to occur because of the possible requirement of high activation energy (Figure 4b). It should be noted that the inlet capillary temperature-dependent behaviors of both reactions could be more complex by the cumulative effect of different properties of the droplet as discussed earlier. Consideration of CID data is intended to interpret the relative stability of the both reactants in the gas phase to corroborate the strikingly different observations of reaction rates on altering the inlet capillary temperature.

CONCLUSIONS

It has been traditional to consider the mass spectrometer to be an ion detector, or more technically, a device that provides the mass-to-charge ratio, m/z, of the bare ion. This passive description of the mass spectrometer can be greatly improved by the new perspective on studying microdroplet chemistry. Our study focused on evaluating the effect of the heated inlet capillary, which is often shown in the past to have no effect on the microdroplet reaction. The possible reasons for rapid quenching of the reaction upon entering the heated capillary inlet were because of the rapid evaporative cooling of the droplets and ejection of bare ions from the droplets. However, the present study reveals two strikingly different observations: the heat of the inlet capillary can accelerate or decelerate the rate of reaction based on the energetics of the reaction. We provide here compelling evidence that the microdroplet reaction can be affected by the inlet capillary temperature caused by competing effects of evaporative cooling of microdroplets and thermal heating of the ejected bare ions of reactants and/or intermediates, both in the heated capillary inlet. If the activation energy of the reaction is sufficiently low, the heating effect can outweigh the cooling effect to continue the reaction in the heated capillary by thermal activation. However, if the activation energy is sufficiently high, the reaction will greatly experience the microdroplet cooling effect causing the reaction rate to be decelerated in the heated inlet capillary.

This study sheds light on better understanding the microdroplet chemistry and the possible effect of the heated capillary inlet on the reaction, making us cautious in tuning this parameter for kinetics and mechanistic studies of microdroplet reactions. One most intriguing question emerging from this study, which requires further exploration in the future, is whether or not a microdroplet reaction can adopt a different pathway by changing the temperature of the heated inlet capillary.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpca.9b05703.

Mass spectra for the microdroplet reactions (PDF)

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Notes

The authors declare no competing financial interest.

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