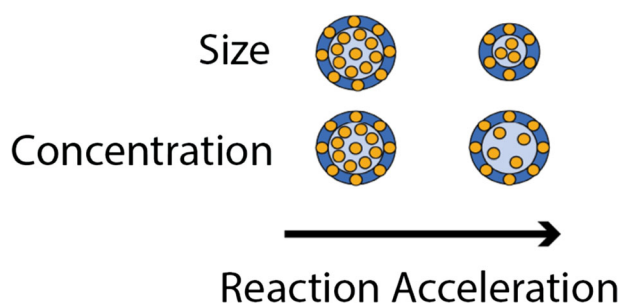


Reaction Acceleration in Electrospray Droplets: Size, Distance, and Surfactant Effects

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Abstract. Phenylhydrazone formation from isatin is used to examine the effects on the reaction rate of (i) electrospray emitter distance from the mass spectrometer (MS) inlet, (ii) emitter tip diameter, and (iii) presence of surfactant. Reaction rates are characterized through measurement of conversion ratios. It is found that there is an increase in the conversion ratio as (i) the electrospray source is moved further from the inlet of the mass spectrometer, (ii) smaller sprayer diameters are

used, and (iii) when surfactants are present. Each of these experimental operations is associated with an increase in reaction rate and with a decrease in average droplet sizes. The size measurements are made using super resolution microscopy from the “splash” on a collector surface produced by a fluorescent marker sprayed using conditions similar to those used for the reaction mixture. This measurement showed that droplets undergo significant evaporation as a function of distance of flight, thereby increasing their surface to volume ratios. Similarly, the effect of nanoelectrospray emitter size on conversion ratio is also found to be associated with changes in droplet size for which a 4 to 10 times increase in reaction rate is seen using tip diameters ranging from 20 μm down to 1 μm . Finally, the effects of surfactants in producing smaller droplets with corresponding large increases in reaction rate are demonstrated by splash microscopy. These findings point to reaction acceleration being strongly associated with reactions at the surfaces of microdroplets.

Keywords: Microdroplets, Reaction acceleration, Microscopy, Hydrazone, Surface reactions

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Introduction

Control of reaction rates is a shared goal of all branches of chemistry. While catalysts and heat [1] have been studied in great detail, recent studies of reactants in microdroplets and thin films suggest that confined reaction volumes too can greatly enhance reaction rates compared with those in bulk

solution [2–5]. A growing body of literature exists which shows that many common organic reactions [6–11] and some inorganic particle formation processes [12] are accelerated in charged microdroplets generated in the course of electrospray and nanoelectrospray ionization (nESI). Despite the growing number of accelerated reactions that have been studied, open questions remain about the origin of the observed acceleration.

In charged microdroplets, reaction rates increase with decreasing droplet size (increasing surface area to volume ratio) [4, 5, 7, 10, 11] implying that the surface of the droplet is intimately involved with the increase in reaction rates observed in these systems. Fluorescence anisotropy measurements of a rhodamine dye in an oil-water emulsion show interfacial enhancement of molecules in droplets, directly implicating a surface-mediated process [13]. The interface of a solution, either with air as in aerosols [14] or levitated droplets [15,

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16], or with a non-miscible solvent as in so-called on-water reactions [17, 18], has a different solvation environment than does bulk solution, in part due to alignment of molecules at the interface [19]. This results in changes in the potential energy surface for reaction [2]. In fact, one suggested explanation of the increased surface reactivity is partial solvation of reactants at the interface [5].

In this work, a series of systematic experiments was performed to elucidate the influence of experimental factors and the underlying causes of reaction acceleration in charged microdroplets produced by nESI. Hydrazone formation from isatin (Scheme 1) [20] was chosen as a model reaction to measure the influence of distance, tip size, and surfactant concentration on reaction acceleration. Super resolution microscopy was used to measure the diameters of droplets of different types [21]; this measurement was made on the droplets after impact on a collector surface. It provides information on the effects of spray tip diameter and evaporation on the size of nESI droplets. Another set of experiments measured the influence of surfactant concentration on the droplet size distribution. Correlation of the distance, tip diameter, and surfactant effects on droplet size, as measured by splash microscopy, provided a picture of microdroplet size effects on reaction acceleration. Initial data on the use of ambient ion focusing on acceleration were taken also, in view of the potential value of such focusing in increasing the scale on which organic synthesis might be performed using nESI sprays [22].

Experimental

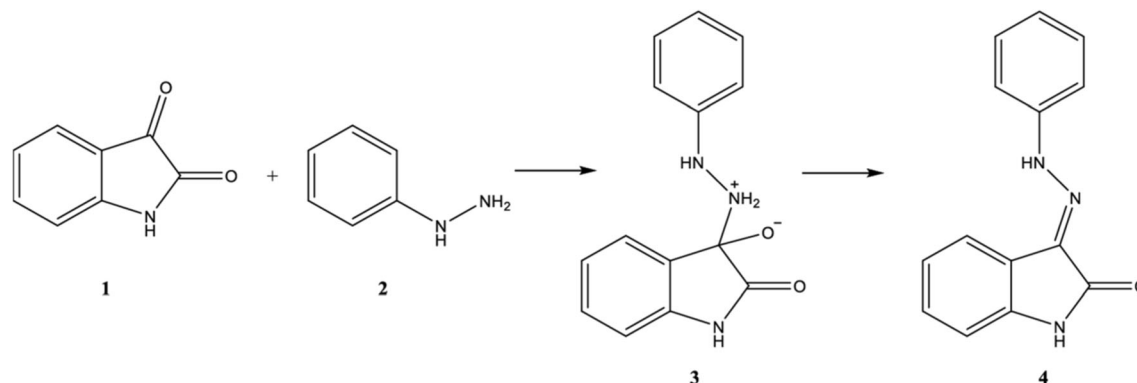
Microscopy

3D structured illumination microscopy (SIM) experiments were performed using a super resolution Nikon Ti-E microscope. The experimental details of this process have been discussed previously [21]. Briefly, a laser light source of 561 nm was used, and the total magnification was $\times 250$. nESI emitters were used as the spray source and a 100 μM Rhodamine B solution in methanol:glycerol 9:1 was used as the spray solution. Previous studies [23] have shown that glycerol-containing droplets measured using the microscopy method

match reasonably well to PDA studies of droplets containing 1:1 water: methanol. This suggests that surface wetting does not change the sizes of the droplets significantly from corresponding air-based measurements. nESI emitters were pulled from borosilicate glass capillaries (0.86 mm I.D., 1.5 mm O.D.) using a micropipette puller to achieve an O.D. of $20 \pm 0.5 \mu\text{m}$ (I.D. estimated at $11 \mu\text{m}$ from initial capillary dimensions). The tip diameters were confirmed by visual observation using a Kronos light microscope equipped with a scale bar. All nESI experiments were performed using a platinum-iridium wire as the electrode. An external voltage of 4 kV was supplied to the emitter from an external high-voltage power supply. The external power supply was connected to a waveform generator to allow pulsed voltages to be applied. Pulsing was performed to avoid the formation of droplet aggregates, which is common with a continuous spray. The pulse duration used for this experiment was 20 ms. Droplets were collected on a grounded indium-tin-oxide (ITO) coverslip (Nano CS, NY, USA) that was approximately 0.16 mm thick and placed in contact with the objective. Two sets of experiments were performed, the first of which measured the effect of distance on droplet size. Distances of 3 mm and 9 mm were used to study the effect of this variable. Note that the distance refers to the distance between the tip of the nanospray emitter and the surface of the coverslip. The second set of experiments measured the effect of the concentration of the surfactant on the droplet size. For both experiments, ten frames were acquired for each setting. For the distance experiments, ten image frames were acquired for each distance and then normalized prior to analysis. A modified circular Hough transformation function in Matlab was used to detect and measure droplet size. An overlap removal algorithm was used to identify incorrectly assigned droplets and remove any overlaps associated with them.

Nanospray Measurements of Reaction Acceleration

Mass spectrometric measurements were performed using an Agilent Ultivo Triple Quadrupole instrument. Briefly, a nESI emitter was connected to an external high-voltage power supply while the inlet capillary of the mass spectrometer was held at 100 V. The DC voltage used for all nESI experiments was



Scheme 1. Formation of 3-(2-phenylhydrazono)indolin-2-one (4) from the reaction of indoline-2,3-dione (1, isatin) with phenylhydrazine (2) in methanol proceeding via reaction intermediate (3)

2 kV. The nESI emitter was positioned at the appropriate distance from the mass spectrometer and the mass spectrum was recorded for 1 min. For the tip size experiments, pulled borosilicate glass emitters with O.D.'s of 1 μm , 5 μm , and 20 μm (estimated I.D.'s of 0.6 μm , 3 μm , 11 μm , respectively) were used, while 5- μm diameter emitters were used for all other mass spectrometry measurements. Reaction mixtures were prepared by mixing 1 mL of 3 mM isatin (**1**) in methanol with 10 μL phenylhydrazine (neat) (**2**). An aliquot (1 μL) of 1 M methanolic HCl was then added to the reaction mixture.

Results and Discussion

Microscopy—Distance Experiments

Previously [21], it was shown that super resolution microscopy can be adapted to measure the sizes of droplets produced via paper spray and nESI. These results indicated that the size of nESI droplets depends on, among other factors, the size of the nESI emitter. As the emitter diameter decreased so did the mean droplet diameter produced during spraying. Measurements at 3-mm distance, with 20- μm O.D. emitters, gave a mean droplet diameter of 1.5 μm and a 5- μm emitter gave a mean droplet diameter around 500 nm. In this work, the influence of spray distance, and by extension droplet flight time, on droplet size was considered. The spray distance refers to the distance between the tip of the nESI emitter and the collection surface and/or the inlet of the mass spectrometer. Figure 1

shows super resolution images of droplets produced by the nESI emitter at 3-mm and 9-mm distances and the corresponding droplet size distributions. The distance from the nESI tip to the surface of the conductive coverslip used as the collector surface was measured using Vernier calipers. Methods used to capture and generate images for the experiments have been described previously [21].

The effect of distance on droplet size can be clearly seen from Figure 1. It should be noted that the frame shown above is one of several and is not representative of the entire droplet plume. Closer distances generate larger droplets while the droplet size decreases as the emitter is moved away from the surface. Larger distances allow greater flight times for the droplets, which in turn provide more time for droplet evaporation. The droplets evaporate until they undergo Coulomb fission, as described by the Rayleigh relation, given as follows:

$$Q_{\text{crit}}^2 = 64\pi\epsilon_0\gamma r^3$$

where Q_{crit} is the critical charge for fission, γ is the surface tension of the droplet solvent, and r is the droplet radius. Coulomb fission serves to further decrease the size of nESI droplets. These results are consistent with observations of droplet evaporation in paper spray and standard ESI [23–25].

Microscopy—Surfactant Experiments

Microscopy experiments were also performed to assess the effect of a typical surfactant, cetyltrimethylammonium chloride

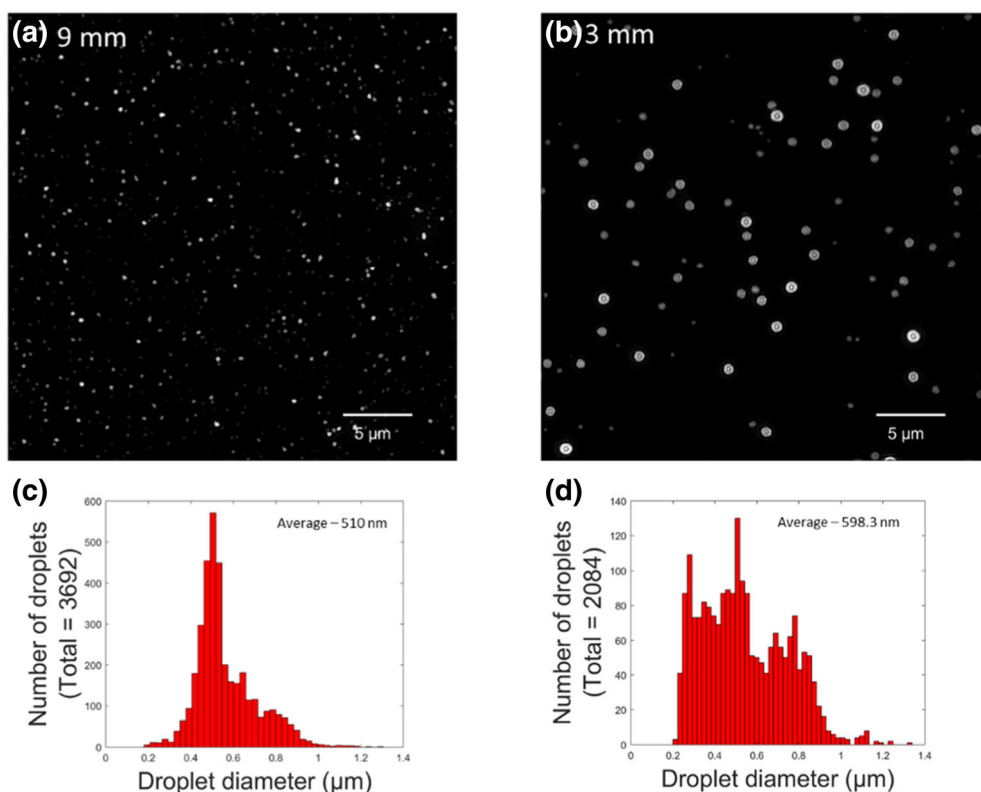


Figure 1. Super resolution microscopy images of 100 μM Rhodamine B in 9:1 methanol:glycerol droplets produced by nESI at distances of (a) 9 mm and (b) 3 mm. Corresponding diameter distributions for (c) 9 mm and (d) 3 mm are also shown

(CTAC), on droplet behavior. A solution of 100 μM Rhodamine B in 9:1 methanol:glycerol containing varying amounts of surfactant (0 mM, 0.1 mM, 1 mM, and 10 mM) was used in all experiments as the spray solution. As shown in Figure 2, as the concentration of the surfactant was increased, the droplet size decreased. While no comparisons could be drawn between this system and known experimental data due to the high phenylhydrazine and glycerol content of the solution, there is significant evidence that, while methanolic solutions are less influenced by surfactants than aqueous solutions, they do experience changes in surface tension [26–28]. Therefore, the decrease in droplet size observed in these experiments is attributed to a change in surface tension, resulting in faster fission of the nESI droplets and lower average droplet diameters.

Effect of Tip Size, Concentration, and Surfactants on Reaction Acceleration

While the previously discussed microscopy experiments provided insight into nESI droplets produced under different conditions, the influence of these conditions on reaction acceleration has not been systematically explored. To investigate these effects, a series of experiments was performed which probe how these factors changed the observed acceleration in a model

hydrazone formation reaction (see Scheme 1) (representative mass spectrum shown in Figure 3a). The reaction solution was mixed and immediately loaded into nESI capillaries with outer diameters of 1, 5, or 20 μm . The solutions were sprayed at various distances from the mass spectrometer inlet to observe reaction progress, as in several previous studies [5, 6, 10, 20]. The extent of reaction progress is given by the conversion ratio, defined as $\frac{I_{238}}{I_{109}+I_{238}} \times 100\%$, where I_{238} is the intensity of the peak corresponding to the hydrazone product (4) and I_{109} is the intensity of the peak corresponding to phenylhydrazine (2).

The resulting measurements (Figure 3B) showed two trends. First, for measurements recorded at the same distance, the conversion ratio fell as the nESI emitter diameter increased. Second, all emitters showed increased conversion at longer distances, with the 1- μm emitter having 73% conversion at 10 cm from the mass spectrometer inlet, while the 20- μm emitter showed only 42% conversion. These results indicated that, all else held equal, smaller initial droplets resulted in greater conversion of reactants to products. It should be noted that droplet size effects have previously been observed in experiments comparing reactive desorption electrospray ionization (DESI) with nESI ionization [4]. Representative error bars have been added to Figure 3B for the 5- μm tip case. These error bars represent the standard error obtained from three

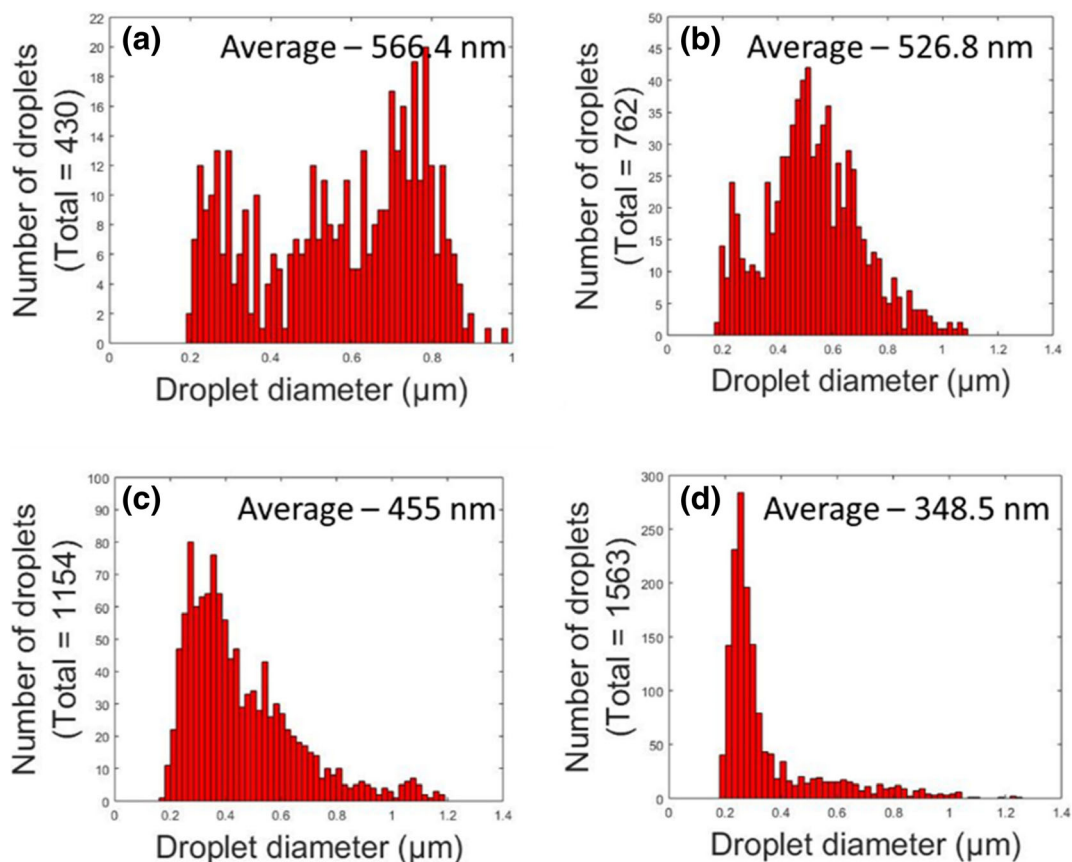


Figure 2. Effect of surfactant on droplet size distribution of a solution containing 100 μM Rhodamine B in 9:1 methanol:glycerol and (a) no surfactant, (b) 0.1 mM surfactant, (c) 1 mM surfactant, and (d) 10 mM surfactant. All experiments were performed using a 20- μs pulse duration and 20- μm nESI tip placed at a distance of 5 mm from the ITO coverslip

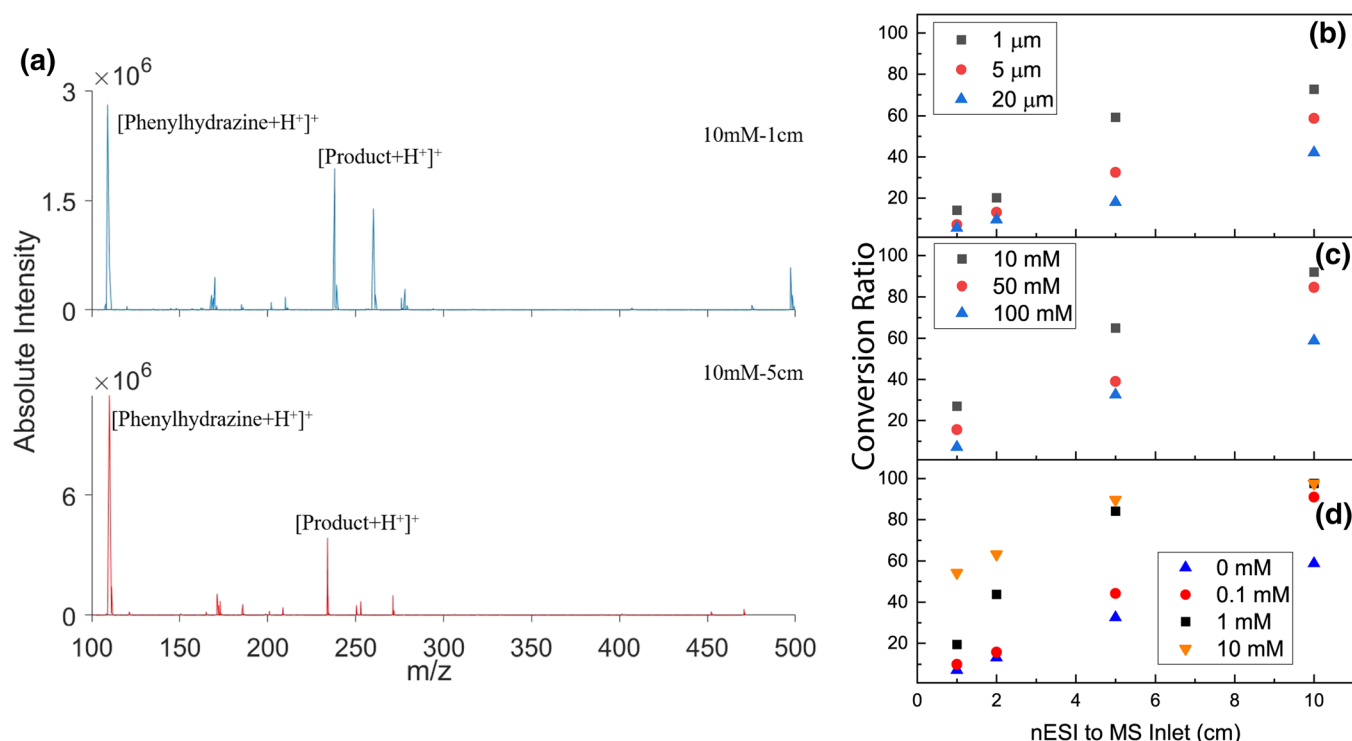


Figure 3. (a) Representative mass spectrum of phenylhydrazine+isatin reaction mixture shown at distances of 1 cm and 5 cm. Effect of (b) tip size (see legend) (c) 10, 50, and 100 mM phenylhydrazine concentrations (shown in legend) with constant isatin concentration and (d) different surfactant concentration (shown in legend) on conversion ratio as a function of emitter to MS distance. Note that the data in panels (b) and (c) were recorded with a 5- μm emitter. Isatin concentration was 3 mM in all measurements here. Methanol was the solvent

separate measurements on different days. Note that, while error does increase with distance, the errors are much smaller than the size of the effects observed here.

Next, the influence of reagent concentration on the conversion ratio was investigated to examine the effect on reaction acceleration. The concentration of isatin was held constant at 3 mM in each measurement while the phenylhydrazine concentration was varied. The data (Figure 3C), recorded using a 5- μm O.D. nESI emitter, showed an inverse relationship between the conversion ratio and phenylhydrazine concentration. As much as 92% conversion was observed for the 10 mM phenylhydrazine solution, and 85% in the 50 mM phenylhydrazine solution, although the maximum conversion observed in the 100-mM case is only around 60% for the 5- μm emitter. Data for other emitter sizes are given in the [Supplemental Information](#). Similar to the tip size study, the conversion ratio was found to increase with distance, although as concentration decreased, the conversion increased for the same distance.

Given that phenylhydrazine is present in excess of the isatin in the above experiment, the effect of increasing both phenylhydrazine and isatin concentrations while maintaining a 1:1 ratio was studied. The data (shown in [SI](#)) indicate that for 10 mM phenylhydrazine/10 mM isatin, the rate is increased significantly relative to the 20 mM phenylhydrazine/20 mM isatin case, at both the distances used. Thus, it is apparent that, in this case, the effect of added concentration is, counterintuitively, to lower the observed rate.

Finally, the influence of surfactant content in the nESI solution was studied. Here, the solutions were made with 0.1 mM, 1 mM, and 10 mM concentrations of CTAC as was done in the corresponding microscopy experiments. The experimental data, taken with a 5- μm O.D. nESI emitter, are shown in Figure 3D. As surfactant concentration was increased, the conversion ratio also increased for an emitter positioned the same distance from the mass spectrometer inlet. Comparison of the 0.1 mM surfactant concentration data with the 0 M surfactant concentration data shows that, while the conversion for the two cases is similar with the nESI emitter close to the mass spectrometer inlet, the curves diverge at long distances, with the 0.1-mM sample showing nearly 100% conversion at 10 cm. In all cases, much higher conversion was observed than in the surfactant-free case.

To investigate the effect of surfactant *charge* on the reaction, the same experiments were performed using sodium lauryl sulfate, putatively a negatively charged surfactant. While the surfactant is likely protonated in the acidic environment of the droplets here, it still stands in contrast to the positive charge of the CTAC surfactant above. It was observed that, for 1 mM and 10 mM concentrations ([SI](#)), the reaction was accelerated by a greater degree than in the CTAC case. While the main effect of surfactant is, we believe, to increase the droplet fission rate, this data indicates that electrostatic effects (which have been shown to be significant in small droplets) [29] from the surfactant molecules may also play a role in the effects observed here.

The reactivity of bulk solutions with and without SLS (SI) shows that the reaction proceeds slightly slower with surfactant compared with the no surfactant case.

To understand why these factors (droplet size, phenylhydrazine concentration, and surfactant concentration) influenced the observed reaction rate, their effects on the electrospray process and droplet dynamics must be understood. While open questions remain about the mechanism of reaction acceleration in microdroplets, it is now clear that the increased reaction rates observed in confined volumes are due, in part, to accelerated reactions that occur at the surface of the droplet [2, 5, 13]. Reagent species located in this region have significantly different solvation environments than those in bulk, meaning that certain species may be stabilized or destabilized at the interface [19, 30], leading to changes in the reaction potential energy surface compared with the bulk case. Thus, the rate constant at the surface may be significantly different than the rate constant in bulk solution. Since the rate constants at the bulk and surface are weighted by the concentrations of molecules in those regions, any increase in surface concentration to bulk concentration ratio can have an outsized effect on the observed reaction rate.

First, the effect of tip size (and by extension the initial droplet size) is considered. For a spherical droplet, the ratio of surface area to droplet volume increases by $\frac{3}{r}$, where r is the radius of the droplet. Thus, as the droplet size is decreased, the “bulk-like” portion of the droplet decreases relative to the volume of the surface. To understand how this influences the relative concentrations of bulk and surface molecules, a model has been developed. Briefly, the model calculates the surface coverage of molecules using an equilibrium surface excess parameter, Γ [31], which represents the propensity of molecules to cover the surface, and to determine which portion of the molecules are adsorbed at the interface vs. being bulk solvated. Details of the calculations are given in the [Supplemental Information](#). It should be noted that this model assumes that the surface will be completely covered by molecules before bulk solvation becomes significant. The volume of the surface layer is determined by multiplying the surface area by a fixed thickness parameter Δr , chosen here to be 0.5 nm, which is on the order of the size of a methanol molecule. A schematic view of the parameters considered is shown in Figure 4a. Note that this model does not consider diffusion to and from the interface.

The surface concentration/bulk concentration ratio for a droplet is plotted as function of droplet radius in Figure 4b. In this case, the solute concentration is taken to be 100 mM, equivalent to the concentration of phenylhydrazine in the tip size experiments. Although the surface excess parameter for this system (phenylhydrazine in methanol) is not known, this model still provides a qualitative picture of molecular partitioning in droplets for surface active species. Here, the Γ value (3×10^{-7} mol/m²) was chosen to represent a case where molecules are preferentially adsorbed at the surface but have a significantly lower surface affinity than surfactant molecules, which typically have a surface excess on the order of 10^{-6} mol/m² [32].

In Figure 4c, the droplet diameter is shown as a function of flight time, using Kebarle and Tang’s model which assumes evaporation in the surface limit [33]. As the droplet radius shrinks, the droplet undergoes fission events, as dictated by the Rayleigh limit. The surface to volume ratio, taking into account evaporation and fission events, as a function of time is shown in Figure 4d, as calculated using the method of Kebarle and Tang [33]. In this model, a parent droplet undergoes fission into 20 smaller offspring droplets containing 15% of the total charge of the parent droplet and having 2% of the total mass of the parent when the droplet reaches 80% of its critical radius, as given by the Rayleigh relation. Here, the surface to volume ratio is evaluated at each droplet fission event as the sum of areas and volumes for the parent droplet and immediate offspring droplets. The droplets have an initial charge equal to 60% of the critical charge for the initial droplet size and have a surface tension equal to that for bulk methanol (22 mN/m).

Comparison of the experimental data with the calculated surface to bulk concentration ratios shows two effects. First, the smaller initial droplets have a slightly higher surface to bulk concentration ratio when they are created, implying that the initial rate is more reflective of the surface reaction rate for such droplets. Second, the calculated evaporation and fission dynamics show that as the droplets undergo evaporation after creation, the surface to volume ratio increases rapidly. This effect is particularly pronounced for the smallest droplets, which see a large increase in surface to volume ratio at earlier times than the large droplets. This observation, taken with the experimental data, suggests that the surface area and surface concentration are key contributors to the observed acceleration with decreasing droplet size.

The same surface concentration model, with a surface excess value of 3×10^{-7} mol/m², is used to evaluate how changes in the initial solution concentration influence the surface to bulk concentration ratio in droplets. The resulting curve, shown in Figure 4e for a 500-nm diameter droplet, indicates that as concentration is decreased, the surface to bulk concentration ratio undergoes a steep increase. This result is reflective of the nature of surface coverage by solute molecules before bulk solvation occurs. The observed rate constant of the reaction depends upon the rate constant of the reaction in the bulk of the droplet and that at the surface of the droplet, as well as the concentrations in these regions. Reduction of the total concentration lowers the bulk concentration while keeping the surface concentration approximately constant, resulting in an increase of the observed (total) rate constant. Again, these results are qualitatively consistent with the experimental data, and further suggest the surface of the droplet is fundamentally important to the high observed reaction rates. This is consistent with the picture promoted by Zare through several recent studies [2, 12, 13, 34] and also with partial solvation as the underlying cause of acceleration, as we have proposed [5, 35].

Finally, the effect of surfactant on the reaction is considered in Figure 5. The influence of surface tension on droplet fission was evaluated using the droplet evaporation model described above. The calculations here use the surface tension of bulk methanol (22 mN/m) as the baseline and a surface tension of 19 mN/m as a

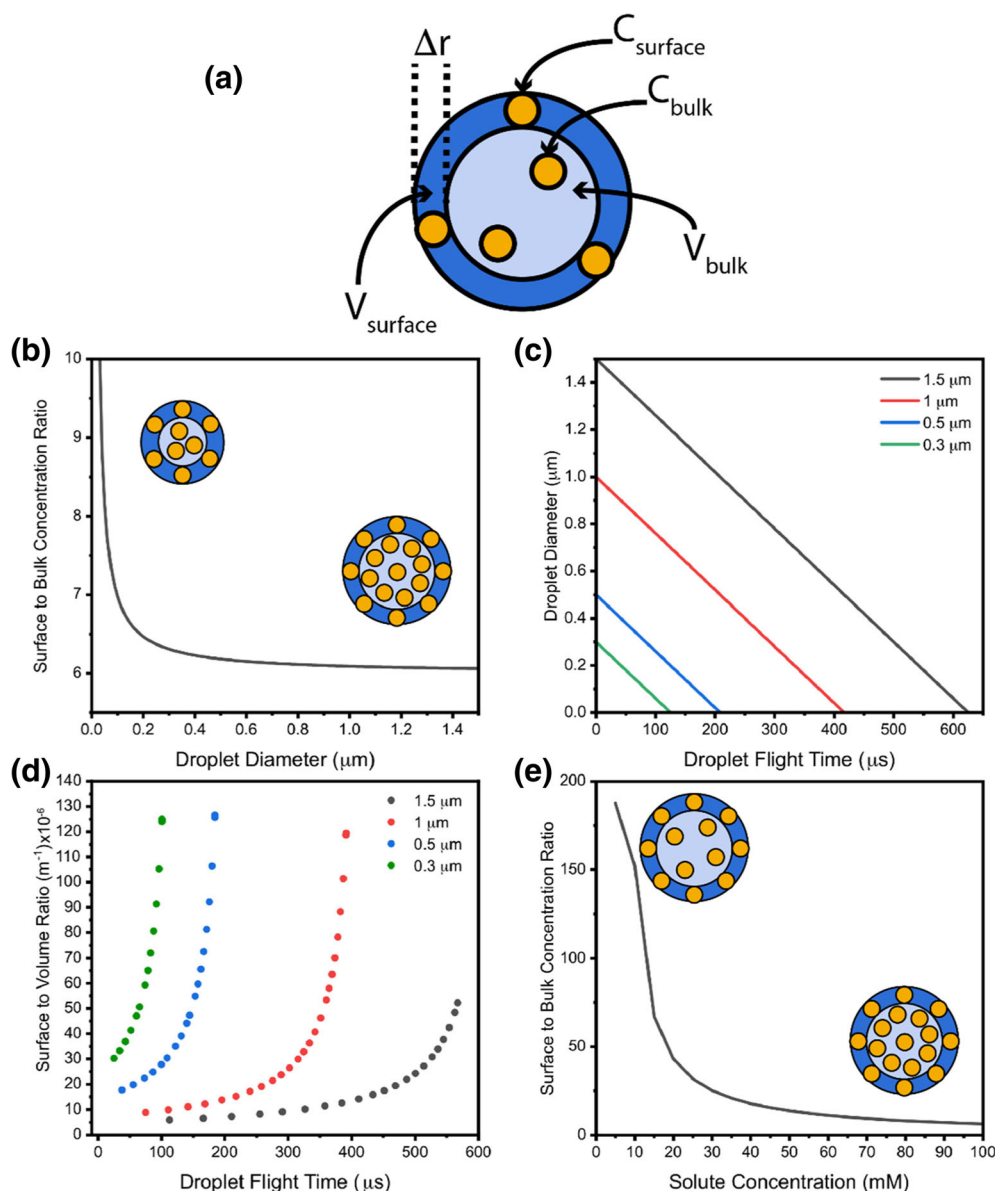


Figure 4. (a) Model of droplet with surface (dark blue) and bulk (light blue) volumes and differing surface and bulk concentrations (molecules represented by orange circles). (b) Relationship between droplet diameter and surface to bulk concentration ratio for a constant concentration of 100 mM solute. Droplet drawings show how volume and concentrations change with diameter. (c) Calculated droplet diameter as a function of droplet flight time. (d) Surface to volume ratio as a function of droplet flight time for different droplet sizes. (e) Surface to bulk concentration ratio for different solute concentrations in a 500-nm diameter droplet. Droplet drawings show the effect of solute concentrations schematically

representative case where surfactant is present. Note that the actual surface tension of this solution is unknown. All calculations are for an initial droplet size of 750 nm with a total charge equal to 60% of the critical charge for the 22 mN/m case (15,239 charges). In the relative surface area graph (Figure 5b), it is assumed that the smaller droplets formed during fission have evaporated between fission events, so the surface area is calculated only considering the parent and immediate offspring droplets.

The surfactant molecules can influence the reaction in two ways. First, the surfactant molecules lower the surface tension of the droplets, which results in droplets undergoing Coulomb

fission earlier than when no surfactant is present, creating more surface area (Figure 5). This effect is clearly observed in the surfactant microscopy data. The second effect is displacement of reagent molecules from the surface by surfactant molecules which would have the opposite effect. At first glance, it is unclear which effect should dominate in a nESI spray. However, each Coulomb fission event results in the creation of multiple droplets which increase the total surface area, lessening the effect of the surfactant coverage. It is clear from examining Figure 5, along with the microscopy data, that the effect of surfactant is primarily to decrease the flight time needed for a droplet to

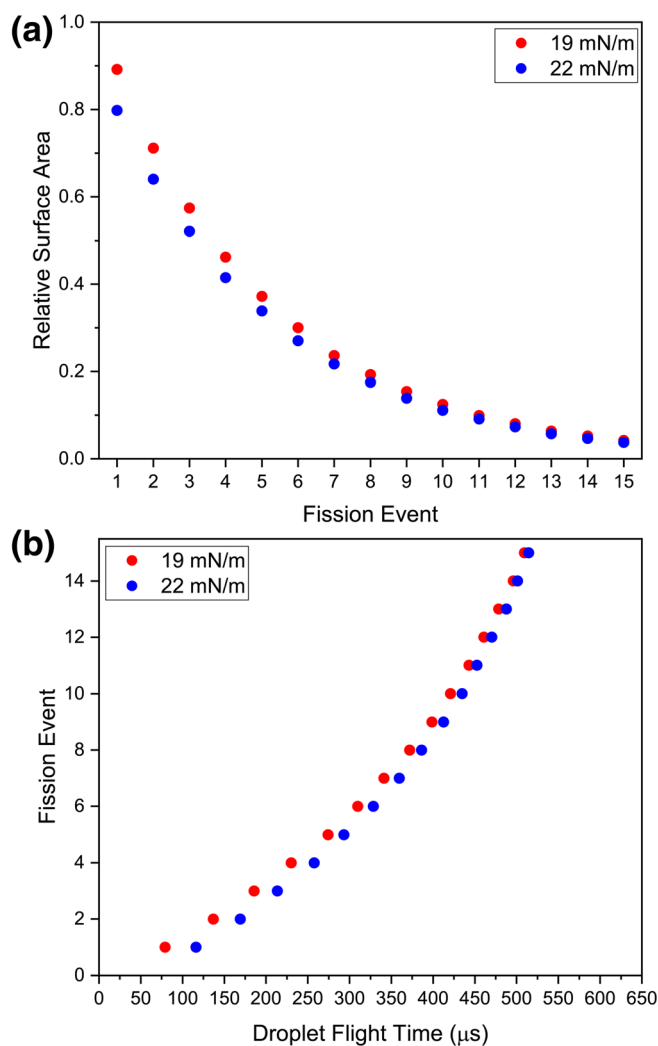


Figure 5. (a) Evolution of surface area with droplet fission event. The surface area at droplet creation is 1. (b) Fission event as a function of droplet flight time for 19 mN/m and 22 mN/m surface tensions

undergo fission, which then results in a higher total surface area at a given time compared with the surfactant-free case. Thus, the dynamic nature of nESI droplets serves to overcome the surface excluding effects of surfactants, further enhancing the reaction rate compared with the no surfactant case. This result stands in contrast with studies of reaction acceleration in Leidenfrost levitated droplets where it has been shown that addition of surfactant to the droplet results in a reduction of the acceleration, implying that exclusion of molecules from the surface of the droplet reduces the rate [36]. Note, however, the Leidenfrost droplets do not fission so the data are entirely consistent.

Applications of Ambient Focusing in Reaction Acceleration

With the establishment of the main facts concerning reaction acceleration, attention can turn towards accelerating reactions on a preparative scale. Several examples already exist in the

literature which demonstrate synthesis on the 10's of milligram scale [37, 38]. One strategy, posited here, is to deposit electro sprayed material onto a collection surface as done in some of the earliest experiments that used acceleration for synthesis [39] but now using a focusing electrode or aperture to increase ion currents. Note that well focused beams (~ 5 mm) of ions can be generated in the open air by the use of DC potentials in ellipsoidally shaped electrodes [40]. An even more straightforward method for producing focused ion beams is to direct the nESI plume through an aperture either floated or held at ground to give a spot up to $10\times$ smaller than the aperture the beam was passed through [41].

We observed the effect of focusing on reaction acceleration at a distance of 5 cm from the nESI emitter to the mass spectrometer inlet using both an ellipsoidal electrode, similar to that discussed in ref. [35], and a 15-mm diameter aperture. In both cases, the electrodes were held at 3 kV, while the sprayer was held at 5 kV to allow sufficient signal for MS analysis. In the case of the ellipsoidal electrode, the emitter was positioned perpendicular to the MS capillary, thus preventing neutral species from being transported. The observed enhancement was similar to that observed by spraying at a 5 kV potential from 5 cm without the use of the electrode. This suggests that focusing itself does not influence the observed degree of reaction acceleration, meaning that the ellipsoidal electrode setup could be employed for surface patterning. Similarly, the aperture experiment showed similar conversion ratios to the case where no aperture was used. Position of the aperture between the MS inlet and nESI emitter did not influence the observed conversion ratio.

Conclusions

In this study, the influence of droplet size, reagent concentration, and surfactant concentration is considered. The evaporative dynamics of microdroplets produced by nESI were followed by super resolution splash microscopy. It was found that over a distance of 6 mm, droplets of methanol undergo significant shrinkage due to evaporation and that the addition of surfactant results in droplet size distributions weighted towards smaller droplets than without surfactants. The influence of these effects, in addition to that of reagent concentration and initial droplet size, was tested on the hydrazone formation reaction. Experiments show that smaller droplets lead to increases in reaction rate, and that a lower concentration of reagent molecules similarly increases the rate. These effects are indicative of a surface reaction occurring in the nESI droplets. Experiments with varying concentrations of surfactant molecules further indicate that smaller droplets enhance reaction rates. The role of diffusion to and from the interface in changing local concentration remains to be determined. No significant changes in acceleration were observed to be associated with ambient ion focusing.

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References

- Schwarz, H., González-Navarrete, P., Li, J., Schlangen, M., Sun, X., Weiske, T., Zhou, S.: Unexpected mechanistic variants in the thermal gas-phase activation of methane. *Organometallics*. **36**(1), 8–17 (2017)
- Mondal, S., Acharya, S., Biswas, R., Bagchi, B., Zare, R.N.: Enhancement of reaction rate in small-sized droplets: a combined analytical and simulation study. *J. Chem. Phys.* **148**(24), 244704 (2018)
- Yan, X., Lai, Y.-H., Zare, R.N.: Preparative microdroplet synthesis of carboxylic acids from aerobic oxidation of aldehydes. *Chem. Sci.* **9**(23), 5207–5211 (2018)
- Girod, M., Moyano, E., Campbell, D.I., Cooks, R.G.: Accelerated bimolecular reactions in microdroplets studied by desorption electrospray ionization mass spectrometry. *Chem. Sci.* **2**(3), 501–510 (2011)
- Yan, X., Bain, R.M., Cooks, R.G.: Organic reactions in microdroplets: reaction acceleration revealed by mass spectrometry. *Angew. Chem. Int. Ed.* **55**(42), 12960–12972 (2016)
- Bain, R.M., Pulliam, C.J., Yan, X., Moore, K.F., Müller, T., Cooks, R.G.: Mass spectrometry in organic synthesis: Claisen–Schmidt Base-catalyzed condensation and Hammett correlation of substituent effects. *J. Chem. Educ.* **91**(11), 1985–1989 (2014)
- Lee, J.K., Kim, S., Nam, H.G., Zare, R.N.: Microdroplet fusion mass spectrometry for fast reaction kinetics. *Proc. Natl. Acad. Sci.* **112**(13), 3898–3903 (2015)
- Bain, R.M., Sathyamoorthi, S., Zare, R.N.: “On-droplet” chemistry: the cycloaddition of diethyl azodicarboxylate and quadricyclane. *Angew. Chem. Int. Ed.* **56**(47), 15083–15087 (2017)
- Lai, Y.-H., Sathyamoorthi, S., Bain, R., Zare, R.: Microdroplets accelerate ring opening of epoxides. *J. Am. Soc. Mass. Spectrom.* **29**, 1036–1043 (2018)
- Bain, R.M., Pulliam, C.J., Cooks, R.G.: Accelerated Hantzsch electrospray synthesis with temporal control of reaction intermediates. *Chem. Sci.* **6**(1), 397–401 (2015)
- Espy, R.D., Wlekinski, M., Yan, X., Cooks, R.G.: Beyond the flask: reactions on the fly in ambient mass spectrometry. *TrAC Trends Anal. Chem.* **57**, 135–146 (2014)
- Lee, J.K., Samanta, D., Nam, H.G., Zare, R.N.: Spontaneous formation of gold nanostructures in aqueous microdroplets. *Nat. Commun.* **9**(1), 1562 (2018)
- Zhou, Z., Yan, X., Lai, Y.-H., Zare, R.N.: Fluorescence polarization anisotropy in microdroplets. *J. Phys. Chem. Lett.* **9**(11), 2928–2932 (2018)
- Dobson, C.M., Ellison, G.B., Tuck, A.F., Vaida, V.: Atmospheric aerosols as prebiotic chemical reactors. *Proc. Natl. Acad. Sci.* **97**(22), 11864 (2000)
- Li, Y., Liu, Y., Gao, H., Helmy, R., Wuelfing, W.P., Welch, C.J., Cooks, R.G.: Accelerated forced degradation of pharmaceuticals in Levitated microdroplet reactors. *Chem. Eur. J.* **24**(29), 7349–7353 (2018)
- Crawford, E.A., Esen, C., Volmer, D.A.: Real time monitoring of containerless microreactions in acoustically levitated droplets via ambient ionization mass spectrometry. *Anal. Chem.* **88**(17), 8396–8403 (2016)
- Narayan, S., Muldoon, J., Finn, M.G., Fokin, V.V., Kolb, H.C., Sharpless, K.B.: “On water”: unique reactivity of organic compounds in aqueous suspension. *Angew. Chem. Int. Ed.* **44**(21), 3275–3279 (2005)
- Fallah-Araghi, A., Meguellati, K., Baret, J.-C., Harrak, A.E., Mangeat, T., Karplus, M., Ladame, S., Marques, C.M., Griffiths, A.D.: Enhanced chemical synthesis at soft interfaces: a universal reaction-adsorption mechanism in microcompartments. *Phys. Rev. Lett.* **112**(2), 028301 (2014)
- Allen, H.C., Casillas-Ituarte, N.N., Sierra-Hernández, M.R., Chen, X., Tang, C.Y.: Shedding light on water structure at air–aqueous interfaces: ions, lipids, and hydration. *Phys. Chem. Chem. Phys.* **11**(27), 5538–5549 (2009)
- Bain, R.M., Pulliam, C.J., Ayrton, S.T., Bain, K., Cooks, R.G.: Accelerated hydrazone formation in charged microdroplets. *Rapid Commun. Mass Spectrom.* **30**(16), 1875–1878 (2016)
- Hollerbach, A., Logsdon, D., Iyer, K., Li, A., Schaber, J.A., Graham Cooks, R.: Sizing sub-diffraction limit electrosprayed droplets by structured illumination microscopy. *Analyst.* **143**(1), 232–240 (2018)
- Wlekinski, M., Falcone, C.E., Loren, B.P., Jaman, Z., Iyer, K., Ewan, H.S., Hyun, S.-H., Thompson, D.H., Cooks, R.G.: Can accelerated reactions in droplets guide chemistry at scale? *Eur. J. Org. Chem.* **2016**(33), 5480–5484 (2016)
- Espy, R.D., Muliadi, A.R., Ouyang, Z., Cooks, R.G.: Spray mechanism in paper spray ionization. *Int. J. Mass Spectrom.* **325–327**, 167–171 (2012)
- Liigand, P., Heering, A., Kaupmees, K., Leito, I., Girod, M., Antoine, R., Kruve, A.: The evolution of electrospray generated droplets is not affected by ionization mode. *J. Am. Soc. Mass Spectrom.* **28**(10), 2124–2131 (2017)
- Soleilhac, A., Dagany, X., Dugourd, P., Girod, M., Antoine, R.: Correlating droplet size with temperature changes in electrospray source by optical methods. *Anal. Chem.* **87**(16), 8210–8217 (2015)
- Bielawska, M., Chodzińska, A., Jańczuk, B., Zdziennicka, A.: Determination of CTAB CMC in mixed water+short-chain alcohol solvent by surface tension, conductivity, density and viscosity measurements. *Colloids Surf. A Physicochem. Eng. Asp.* **424**, 81–88 (2013)
- Verrall, R.E.: Kinetics studies of alcohol–surfactant mixed micelles. *Chem. Soc. Rev.* **24**(2), 135–142 (1995)
- Burrows, J.C., Flynn, D.J., Kutay, S.M., Leriche, T.G., Marangoni, D.G.: Thermodynamics in surfactant solutions: determination of the micellization enthalpy and entropy of alcohol/surfactant mixed micelles. A comparison of calorimetric methods with temperature differentiation of the $\ln X_{cmc}$ values. *Langmuir.* **11**(9), 3388–3394 (1995)
- Chen, Y., Okur, H.I., Lütgebaucks, C., Roke, S.: Zwitterionic and charged lipids form remarkably different structures on nanoscale oil droplets in aqueous solution. *Langmuir.* **34**(3), 1042–1050 (2018)
- Gopalakrishnan, S., Liu, D., Allen, H.C., Kuo, M., Shultz, M.J.: Vibrational spectroscopic studies of aqueous interfaces: salts, acids, bases, and nanodrops. *Chem. Rev.* **106**(4), 1155–1175 (2006)
- Mitropoulos, A. Ch.: What is a surface excess? *J. Eng. Sci. and Tech. Rev.* **1**(1), 1–3 (2008)
- Wang, C., Morgner, H.: The dependence of surface tension on surface properties of ionic surfactant solution and the effects of counter-ions therein. *Phys. Chem. Chem. Phys.* **16**(42), 23386–23393 (2014)
- Tang, L., Kebarle, P.: Dependence of ion intensity in electrospray mass spectrometry on the concentration of the analytes in the electrosprayed solution. *Anal. Chem.* **65**(24), 3654–3668 (1993)
- Nam, I., Nam, H.G., Zare, R.N.: Abiotic synthesis of purine and pyrimidine ribonucleosides in aqueous microdroplets. *Proc. Natl. Acad. Sci.* **115**(1), 36 (2018)
- Li, Y., Yan, X., Cooks, R.G.: The role of the Interface in thin film and droplet accelerated reactions studied by competitive substituent effects. *Angew. Chem. Int. Ed.* **55**(10), 3433–3437 (2016)
- Bain, R.M., Pulliam, C.J., Thery, F., Cooks, R.G.: Accelerated chemical reactions and organic synthesis in Leidenfrost droplets. *Angew. Chem. Int. Ed.* **55**(35), 10478–10482 (2016)
- Iyer, K., Yi, J., Bogdan, A., Talaty, N., Djuric, S.W., Cooks, R.G.: Accelerated multi-reagent copper catalysed coupling reactions in micro droplets and thin films. *React Chem Eng.* **3**(2), 206–209 (2018)
- Wei, Z., Wlekinski, M., Ferreira, C., Cooks, R.G.: Reaction acceleration in thin films with continuous product deposition for organic synthesis. *Angew. Chem.* **129**(32), 9514–9518 (2017)
- Badu-Tawiah, A.K., Campbell, D.I., Cooks, R.G.: Accelerated C–N bond formation in dropcast thin films on ambient surfaces. *J. Am. Soc. Mass Spectrom.* **23**(9), 1461–1468 (2012)
- Baird, Z., Peng, W.-P., Cooks, R.G.: Ion transport and focal properties of an ellipsoidal electrode operated at atmospheric pressure. *Int. J. Mass Spectrom.* **330–332**, 277–284 (2012)
- Anyin, L., Zane, B., Soumabha, B., Depanjan, S., Anupama, P., Thalappil, P., Graham, C.R.: Using ambient ion beams to write nanostructured patterns for surface enhanced Raman spectroscopy. *Angew. Chem.* **126**(46), 12736–12739 (2014)