Accelerated Chemical Reactions and Organic Synthesis in Leidenfrost Droplets

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In memory of Klaus Biemann

Abstract: *Leidenfrost levitated droplets can be used to accelerate chemical reactions in processes that appear similar to reaction acceleration in charged microdroplets produced by electrospray ionization. Reaction acceleration in Leidenfrost droplets is demonstrated for a base-catalyzed Claisen–Schmidt condensation, hydrazone formation from precharged and neutral ketones, and for the Katritzky pyrylium into pyridinium conversion under various reaction conditions. Comparisons with bulk reactions gave intermediate acceleration factors (2–50). By keeping the volume of the Leidenfrost droplets constant, it was shown that interfacial effects contribute to acceleration; this was confirmed by decreased reaction rates in the presence of a surfactant. The ability to multiplex Leidenfrost microreactors, to extract product into an immiscible solvent during reaction, and to use Leidenfrost droplets as reaction vessels to synthesize milligram quantities of product is also demonstrated.*

Electrospray ionization (ESI) is a commonly used ionization technique for mass spectrometry (MS) in which analyte ions are generated and transferred from solution into the gas phase. In ESI, analytes in a charged solution are sprayed pneumatically to produce a plume of charged microdroplets. These droplets undergo desolvation and Coulombic fission events to produce numerous smaller and more concentrated droplets.[1] These microdroplets are the nexus for accelerated chemical reactions.[2] On-line monitoring experiments have demonstrated that increasing the distance between the sprayer and the MS increases the product to starting material ratio, indicating the occurrence of rapid reactions in the droplets.[3] Zare and co-workers demonstrated that the reaction rate acceleration in the spray (compared to the bulk) for the Pomeranz–Fritsch synthesis of isoquinoline was more than six orders of magnitude.[4] In a study of the base-catalyzed Claisen–Schmidt condensation, we showed that acceleration is not simply a result of increased concentration but is influenced by interfacial effects.[5] Successful efforts at

milligram scale synthesis using reactions in electrosprayed droplets have also been reported using multiplexed ESI emitters.[6]

The Leidenfrost effect, discovered in 1756, occurs when a liquid is dropped on a surface that is heated to a temperature significantly higher than the boiling point of the liquid (Figure 1). As the droplet approaches the heated surface, an
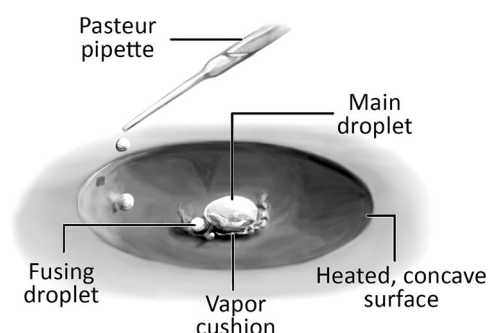

Figure 1. The Leidenfrost reaction system used in these experiments. Additional reaction mixture was added with a pipette to keep the volume of the Leidenfrost droplets constant. The added droplets impact the surface and fuse with the main levitated droplet, which sits atop a cushion of solvent vapor.

insulating vapor layer is formed that keeps the solution from boiling rapidly.[7] With this vapor cushion in place, the droplet levitates, and solvent gradually evaporates. The Leidenfrost phenomenon has been used as a method of thermal desorption employing dielectric barrier discharge ionization to record mass spectra.[8] Leidenfrost droplets have also been used as microreactors for the preparation of metal nanoparticles;[9] for example, Park and co-workers used this technique to prepare nanoporous Pd by placing a $Pd(NO_3)_2$ solution onto a hotplate and allowing the droplet to completely evaporate, leaving Pd black.[9b] Inverse Leidenfrost experiments have also been performed by levitating droplets on liquid nitrogen.[10] For traditional Leidenfrost droplets, the vapor pressure and droplet evaporation processes have been well characterized.[11] Furthermore, Leidenfrost droplets have been shown to have localized pH extremes within the droplets.[8] Herein, we demonstrate the use of the Leidenfrost effect to perform accelerated chemical synthesis in droplets. We show that interfacial effects are involved in acceleration and prepared macroscopic amounts of synthetic products within minutes.

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Droplet levitation and manipulation techniques have been characterized using high electric fields in field-induced droplet ionization (FIDI) experiments. This technique dates back nearly a century and was initially applied to neutral droplets.[12] Later, Grimm and Beauchamp reported the use of strong electric fields to extract positive and negative ions from neutral droplets.[13] Further work was performed with on-line FIDI-MS to study the chemistry at the air–droplet interface.[14] Smith and co-workers have used similar contactless droplet levitation techniques making use of acoustic waves to study the fundamentals of ionization and the properties of the air–water interface.[15]

Hydrazone formation between cortisone (**1**) and Girard's Reagent T (**2**) to form the precharged hydrazone product **3** (Scheme 1) was selected as a model reaction because a similar
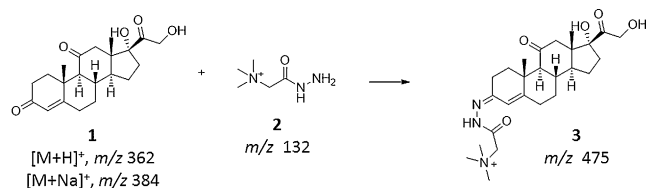
Scheme 1. Cortisone (**1**) and Girard's reagent T (**2**) react to form hydrazone **3**.

system has been characterized in the bulk phase and also by using acceleration in desorption electrospray ionization (DESI) droplets.[16] The results (Table 1) show significant reaction acceleration, expressed as an acceleration factor, which was defined as the ratio of the MS product ion signal to the reagent ion signal in the Leidenfrost droplet versus the ratio in the bulk experiment. This ratio of ratios is a crude

measure of reaction rate acceleration as it does not take into account ionization efficiency differences, amongst other factors. Acceleration factors were measured from the product/reagent ratios for the Leidenfrost reaction with the 5 mM solution vs. 20 mM bulk solution (to account for the concentration increase in the Leidenfrost droplets that is due to evaporation). The result is a product (**3**)/reagent (**1**) ion ratio that is notably higher (by a factor of 4) than that for the bulk solution (see the Supporting Information, Section S4). The addition of acid increases product formation in both experiments. The acceleration is also evident from the fact that the product/reactant ratio in the Leidenfrost droplets after 2 min (0.4) approximately matched that (0.6) reached after 1 h in the corresponding bulk experiment (Table 1).

The reaction of neutral isatin (**4**) with phenylhydrazine (**5**) to form hydrazone **7** via an observable precondensation intermediate **6** (Scheme 2) was also investigated. This reaction is known to be accelerated in the charged droplets generated by nESI when the distance between the spray source and the MS inlet is increased. This is ascribed to solvent evaporation and increased analyte concentrations as well as to increased surface/volume ratios.[17] The Leidenfrost version of this reaction also showed a substantial acceleration
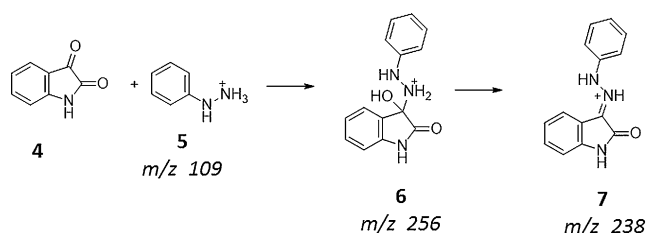
Scheme 2. Reaction of **4** and **5** to form hydrazone **7** via intermediate **6**.

Table 1: Bulk-phase and Leidenfrost droplet reactions and acceleration factors (acc. factors).

Girard T/Hydrazine Reaction Products 3/1 Ratio of ion intensities								Phenylhydrazine/Isatin Reaction Products 7/5 Ratio of ion intensities			
Reaction time (min)	x4 Bulk	x4 Bulk, add'l acid	LF Droplet	x1 Bulk	LF Droplet, add'l acid	x1 Bulk add'l acid		Reaction time (min)	x4 Bulk	LF Droplet	x1 Bulk
2	0.1	0.5	0.4	0.05	1.0	0.06		2	0.05	0.3	0.03
60	0.6	2.0	Acc. factor: 4		Acc. factor: 2			60	0.1	Acc. factor: 6	
120	1.0	2.8						120	0.2		
180	3.2	3.4						180	0.3		

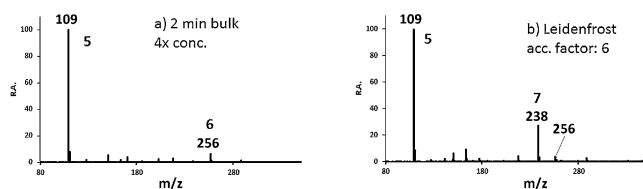| Katritzky Reaction Products 10/8 Ratio of ion intensities								Claisen-Schmidt Reaction Products 13/11 Ratio of ion intensities			
Reaction time (min)	x4 Bulk	x4 Bulk with base	LF Droplet	x1 Bulk	LF Droplet with base	x1 Bulk with base		Reaction time (min)	x4 Bulk	LF Droplet	x1 Bulk
2	0.1	0.4	0.8	0.05	20	0.2		2	0.6	10	0.25
60	0.2	0.8	Acc. factor: 8		Acc. factor: 50			60	3.3	Acc. factor: 17	
120	0.5	2.1						120	10		
180	0.6	10						180	18		

Figure 2. The bulk-phase reaction of **4** and **5** showed mainly reagent **5** and a small amount of intermediate **6** after 2 min (a) whereas the parallel Leidenfrost experiment led to significant product (**7**) formation (b).

factor (× 6 after correction for concentration effects) over the bulk phase reaction (Table 1 and Figure 2).

The Katritzky reaction (Scheme 3) of 2,4,6-triphenylpyrylium (**8**) with 4-methoxyaniline (**9**) to yield the corresponding
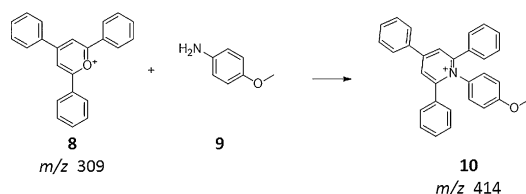
Scheme 3. The pyrylium cation **8** reacts with 4-methoxyaniline (**9**) to produce pyridinium cation **10**.

pyridinium cation **10** was also investigated. This base-catalyzed reaction has previously been investigated by paper spray ionization (thin-film experiment), and showed a significant reaction acceleration.[18] The reaction (2 min, constant volume by addition of reaction solution) in Leidenfrost droplets showed acceleration factors of 50 and 8 for the reactions performed with and without the base catalyst, respectively (Figure 3, Table 1). Note that the time taken for the bulk reaction to reach the same product/reagent ion intensities (an alternative measure of the acceleration factor) is > 10 h vs. the 2 min Leidenfrost time.

The potential for scaling up of Leidenfrost reactions was explored using the Katritzky reaction. In a prototype experi-
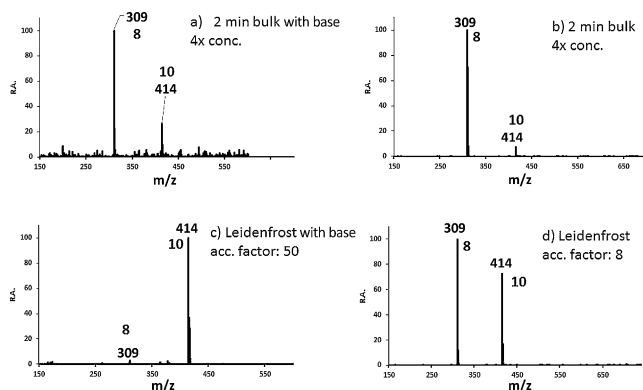
ment, eight ceramic spacers were used to isolate eight Leidenfrost droplets and keep them from fusing. The droplets were levitated for approximately 2 min while their individual volumes (0.5 mL) were maintained by pipetting in fresh reaction mixture. When the spacers were removed to allow the droplets to fuse, a single large droplet formed, and it was immediately extracted from the surface with a pipette. The resulting sample (18 mg) was analyzed by MS and found to be 90% pure by standard addition of reagent **8** (10% unconverted **8**). This simple experiment illustrates the ease of manipulating these droplets, multiplexing this mesoscale reactor system, and synthesizing organic compounds on the milligram scale. The Supporting Information (Section S5) includes an image of the multiplexed experimental setup.

One feature of Leidenfrost droplets is reaction acceleration. Another is the ability to use immiscible solvents and so to perform liquid/liquid extractions in the reacting solution, removing product as it is formed and so driving the reaction. This capability was demonstrated by the base-catalyzed aqueous hydrolysis of adipic acid monoethyl ester (Section S1). The ester was placed in a chloroform droplet that was levitated in contact with a methanol/water droplet containing base. The data in the Supporting Information indicate extensive hydrolysis with product transfer into the aqueous phase during the reaction (Section S6).

Lastly, a base-catalyzed Claisen–Schmidt condensation was investigated because the acceleration of this reaction has been well-characterized by paper spray and ESI.[5,19] 6-Hydroxy-1-indanone (**11**) was reacted with benzaldehyde (**12**) in the presence of base to form the condensation product **13** (Scheme 4). Both the starting material (**11**) and the
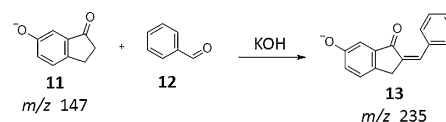
Scheme 4. Condensation of **11** and **12** to form product **13**, examined in the negative-ion mode.

product (**13**) are presumably deprotonated at the aromatic hydroxy group and have similar ionization efficiencies in the negative-ion mode. The peak intensities in the mass spectra (Figure 4) reflect the extent of the reaction, which is significantly greater for the Leidenfrost experiment than in the bulk phase (acceleration factor: 17).

To explore the role of the surface in Leidenfrost droplet acceleration, surfactants were added to the reaction mixture. The addition of triton X-100 (Section S7) had a significant effect on reaction acceleration. The addition of 0.01% (v/v) triton had no effect, but a 1% (v/v) triton-containing reaction mixture, when subjected to the same Leidenfrost conditions, showed significant suppression of acceleration (Figure 4), whereas 5% (v/v) triton suppressed the reaction to bulk values. Higher concentrations of triton did not allow the droplet to be maintained at the Leidenfrost temperature. A blank bulk-phase experiment with 1% triton showed no change in the extent of acceleration. These experiments

Figure 3. Bulk-phase Katritzky reactions with and without base ((a) and (b)) gave smaller product (**10**) versus starting material (**8**) ratios than the corresponding Leidenfrost experiments ((c) and (d)), which displayed acceleration factors of 50 and 8, respectively.
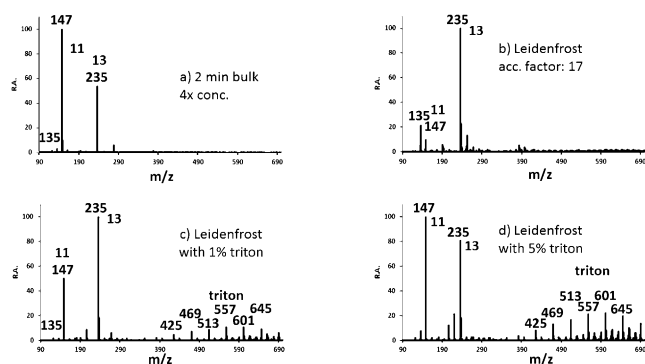
Figure 4. Surface effects in Claisen-Schmidt reactions. a) The **13**/**11** ratio in the bulk-phase reaction after 2 min. b) The **13**/**11** ratio in the Leidenfrost reaction, showing an acceleration factor of 17. The addition of triton X-100 at 1% and 5% v/v suppressed the acceleration effect to factors of just 2 and 1 as shown in (c) and (d), respectively. The *m/z* peaks with a spacing of 44 are PEG-spaced peaks of triton.

demonstrate the role of the surface in the acceleration of these reactions as small concentrations of triton block the surface and diminish accelerated product formation. Further experiments on the role of the concentration and details of the Leidenfrost methods can be found in the Supporting Information, Section S8.

Heat is also a factor in promoting reactions in Leidenfrost droplets and has been investigated as a potential source of acceleration. The temperatures in Leidenfrost droplets are not well characterized, but there is significant mixing and a temperature approximately 10–20°C below the boiling point of the solvent is considered to be an acceptable approximation.[9] The effect of temperature was examined by performing the Claisen–Schmidt condensation in bulk at 45°C in methanol (methanol boils at 65°C). The increased temperature provided an acceleration factor of just 2. Even when the same reaction was performed under reflux, that is, at temperatures well above those in Leidenfrost droplets, the acceleration factor was only 5 (significantly less than the acceleration factor of 17 seen for the Leidenfrost droplet).

In conclusion, the use of Leidenfrost droplets for small-scale synthesis has been demonstrated through simple examples, and a variety of chemical reactions have been accelerated. The observed acceleration is modest by comparison with that seen in the much smaller droplets generated by ESI, which is consistent with the smaller surface/volume ratios of the larger droplets and with the role played by the interface in reaction acceleration. Direct evidence for surface reactions was obtained by experiments with added surfactant. Concentration and temperature effects also play a role in reaction acceleration. This study suggests that Leidenfrost droplets can be used to screen reactions and create milligram quantities of material in minutes.

Experimental Section

The Leidenfrost droplets were maintained at a constant volume of ca. 0.5 mL (orders of magnitude larger than the submicrometer diameter droplets of ESI) by adding approximately 2 mL of the reaction mixture in aliquots over the 2 min course of droplet levitation (Figure 1). The volume was kept constant by monitoring the diameter of the droplet over the time course of the experiment using a scale bar. As the droplets concentrate the reaction mixture by a factor of approximately four over the initial concentration during the constant-volume experiment, bulk-phase reactions were also performed at fourfold higher concentrations to correct for the concentration effect. Additional experiments were performed in which a constant volume was maintained by addition of pure solvent. Comparisons to bulk reactions were performed at room temperature at the initial concentrations used for the Leidenfrost experiments. These additional experiments helped separate effects of concentration changes from those associated with other features of the levitated droplets, notably interfacial effects.

Leidenfrost experiments were conducted for 2 min in a Petri dish atop a heater/stirrer with a surface temperature between 400 and 500°C. All analyses were performed by nanoESI using an LTQ XL-Orbitrap hybrid mass spectrometer (Thermo Fisher Scientific, San Jose, CA). Additional experimental details on each reaction system can be found in the Supporting Information, Section S1. All reagents and solvents were purchased from Sigma–Aldrich (St. Louis, MO) unless otherwise specified. The determination of the acceleration factors and the nESI-MS method used for chemical analysis are discussed in the Supporting Information, Sections S2 and S3.

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Angew. Chem. Int. Ed. **2016**, *55*, 10478–10482