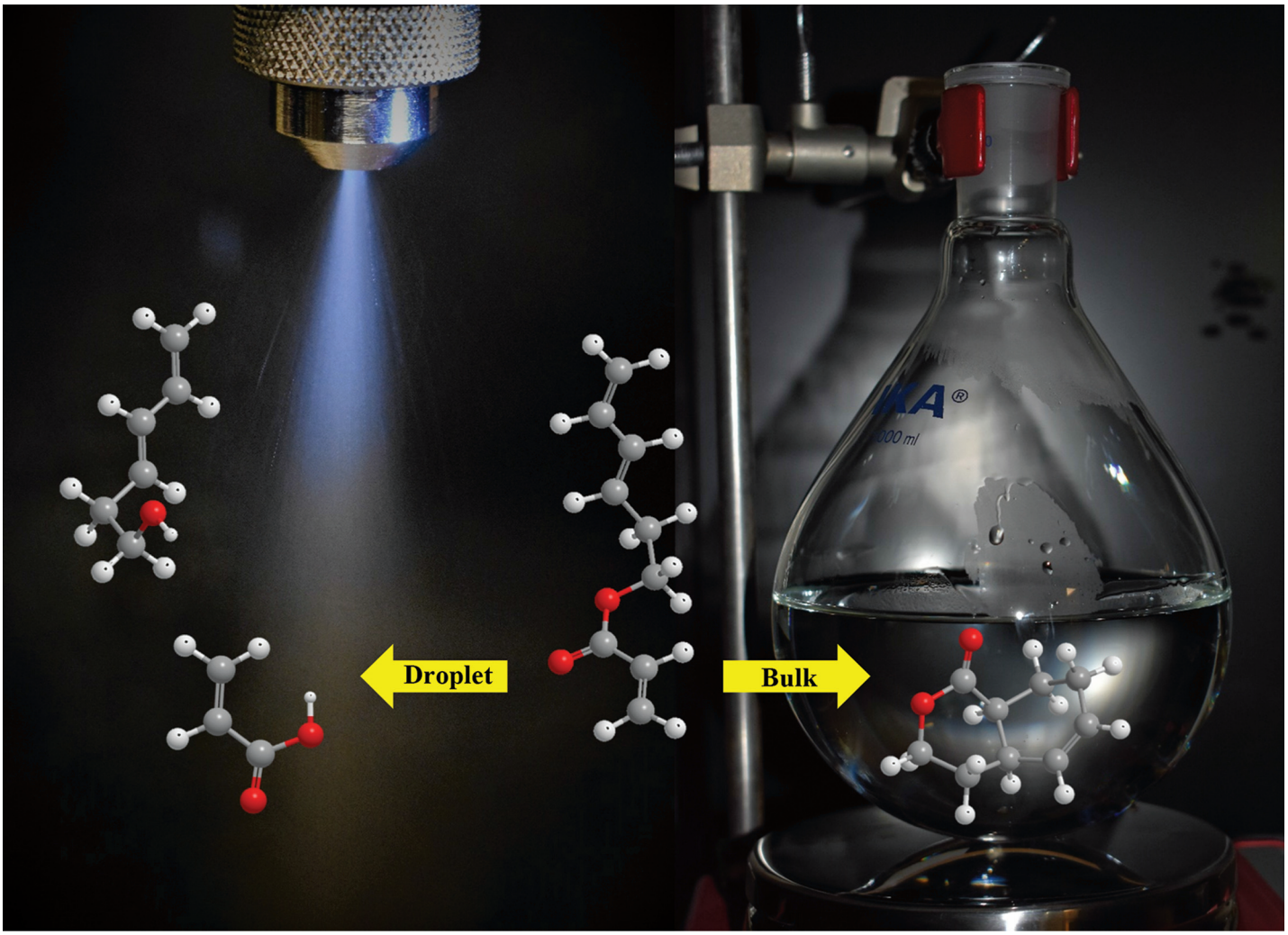

Showcasing how reactions in microdroplets can markedly differ from those in bulk solution, from the team of Professor Richard N. Zare, Department of Chemistry, Stanford University, Stanford, California USA.

Can all bulk-phase reactions be accelerated in microdroplets?

In microdroplets, reactions occur primarily at or near the surface and can be strongly influenced by charges that are preferentially accumulated there. This finding can be important in understanding the chemical analysis of microdroplet reactions.

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Can all bulk-phase reactions be accelerated in microdroplets?

Shibdas Banerjee, Elumalai Gnanamani, Xin Yan and Richard N. Zare *

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Recent studies have shown that microdroplet reactions are markedly accelerated compared to the corresponding bulk-phase reactions. This raises the question whether all reactions can be sped up by this means. We present a counter example, and we show that the reaction mechanism in microdroplets can differ sharply from that in bulk, especially because of the distinct microdroplet surface environment. This analysis helps to guide us how to choose and control reactions in microdroplets and provides a possible perspective on utilizing microdroplet chemistry to scale up synthesis.

Much excitement has met the news that a number of bulk-phase reactions can be dramatically accelerated in microdroplets.[1] These findings have stimulated many analytical studies to learn about reaction intermediates.[2–4] There is also interest in microdroplet chemical synthesis[5,6] because it is envisioned as a powerful method for performing reactions that show extremely slow kinetics in the bulk phase. Although a number of alternative methods, such as sonication- and microwave-assisted synthesis,[7,8] have been undertaken to speed up reactions, microdroplet synthesis is of potential interest particularly because of the gentleness of the process, which can even be environmentally benign by using an aqueous solvent.

In the last few years, a number of reports from the Cooks' group,[1,5,6,9,10] ourselves,[3,4,11] and others[1,12–17] have substantiated the usefulness of microdroplets in conducting many kinds of analytical analyses and organic reactions: the latter includes addition reactions,[9,18] condensation reactions,[5,6,9,18] elimination reactions,[1] substitution reactions,[1] redox reactions,[11] rearrangement reactions,[3] and noncovalent complexations.[4,11] Table 1 lists some examples of different types of reactions studied in microdroplets, which showed remarkable acceleration of the reaction rate by many orders of magnitude when compared to the conventional bulk-phase synthesis. For example, the bulk-phase Pomeranz–Fritsch synthesis of isoquinoline is known to take a long time (few days) and to require very high acid concentrations.[19] In sharp contrast we recently showed clear evidence that the same reaction occurs on the millisecond timescale in droplets from an electrospray ionization (ESI) source without the addition of any external acid.[3] Therefore, the Pomeranz–Fritsch synthesis of isoquinoline can occur at more than a million times faster rate in the charged microdroplets than that in the bulk phase.

Table 1 Some examples of reaction rate acceleration in microdroplets

#	Reaction	Method	Acceleration factor
1	Reaction of Girard's reagent T with ketosteroids	Reactive DESI[9]	$\sim 10^2$
2	Base catalyzed Claisen–Schmidt condensation of 1-indanone	ESI[6]	$\sim 10^4$
3	Hantzsch synthesis of 1,4-dihydropyridines	ESI[5]	$\sim 10^5$
4	Imine synthesis	Emulsion droplet[14]	~45
5	Reduction of 2,6-dichlorophenolindophenol (DCIP) by ascorbic acid	Microdroplet fusion[11]	$\sim 10^3$
6	Noncovalent complexation between cytochrome *c* and maltose	Microdroplet fusion[4]	$\sim 10^3$
7	Pomeranz–Fritsch synthesis of isoquinoline	ESI[3]	$>10^6$
8	Friedländer synthesis of a substituted quinoline	ESI[3]	$>10^5$
9	Combes quinoline synthesis	ESI[3]	$>10^3$

A tantalizing question is whether the study of microdroplet reactions can reveal the mechanism of how reactions occur in bulk. Certainly, this was the initial hope of this research group. On studying all these reactions (Table 1), however, it has become apparent that the environment in microdroplets is strikingly different from that of the corresponding bulk phase. How exactly the reaction is facilitated in microdroplets is still not unambiguously known as there are supposed to be many factors that contribute to the reaction rate acceleration. Although the microdroplet evaporation and confinement of reagents could successfully explain the reaction rate enhancement of a bimolecular reaction by the concentration effect, it

Department of Chemistry, Stanford University, Stanford, CA 94305, USA.
E-mail: zare@stanford.edu

fails to explain the reaction rate acceleration of a unimolecular reaction, which should not be strongly sensitive to the reagent concentration. Likewise, reported literature studies also demonstrate that the unimolecular process of protein/peptide folding or unfolding (conformational change) in nanodroplets should not be affected by the concentration changes caused by solvent evaporation.[15–17] Furthermore, the reagent concentration can also be increased in the bulk phase but this is not expected to achieve the dramatic increase of the reaction rate found using microdroplets. Possibly, one of the most important features of microdroplets is the high surface-to-volume ratio providing a unique polar surface environment for a reaction to occur at or near the air–liquid interface. Indeed, if one liter liquid is sprayed to form an aerosol and assuming the average radius of the aerosol microdroplet is 1 μm, the aerosol should provide a total surface area around 3×10^3 m^2, which is significantly higher than the surface of the liquid in a one-liter flask. If the microdroplet is provided a net charge by the ESI process,[20] this should again contribute to the alteration of pH of the microdroplet surface, whether the microdroplet is composed of water or one of the common organic solvents, such as methanol or acetonitrile. Therefore, it can be anticipated that the polar reagents should be highly surface active for acid- or base-catalyzed reactions on the polar microdroplet surface. Indeed, in our earlier report we presented that decreasing the droplet size and increasing the charge (protons) of the ESI-generated microdroplets both strongly contribute to the reaction rate acceleration of some acid-catalyzed reactions, suggesting that these reactions occurred in a confined environment on the charged surface of the microdroplet.[3] As the ESI-generated microdroplet protons are produced by solvent oxidation, and unlike normal Brønsted acids, they lack counterions (conjugate bases), they are anticipated to be powerful acids to promote these reactions and cause the reaction to be much faster than that in the conventional bulk phase. Moreover, solvation at the surface is not expected to be the same as solvation in the microdroplet core. Therefore, the possibility of contact ion pairing of the protonated species with the anion (if any) is more prominent in the core than at the surface. Smid has pointed out that loose or solvent-separated ion pairs may be many times more reactive than contact ion pairs.[21,22] This fact may also contribute to enhancing the reaction rate at the microdroplet surface. Apart from these effects, reactions conducted by using the ESI process can also be affected by microdroplet jet fission (asymmetric Coulomb fission) and the large electrostatic pressure experienced by the nanodroplet surface, especially at the late stages of the evolution process. The orientation of the reagent molecule on the microdroplet surface caused by the interfacial electric field can also affect the reaction rate. In addition, the microdroplet solvent composition is known to contribute to the reaction rate.[4] Therefore, it seems reasonable to consider the cumulative effects of multiple parameters (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) affecting the reaction rate in the microdroplet although one parameter might outweigh other parameters depending upon the type of reaction being studied.

An important question that we are addressing here is whether or not all bulk-phase reactions can be accelerated in microdroplets. So far, most of the microdroplet studies reported are of specific types, *e.g.*, either they are acid- or based-catalyzed reactions and/or the reactants contain reactive polar functional groups like amines, aldehydes, and ketones (Table 1).[1] It seems that no information is known about the reaction of a nonpolar compound in microdroplets. In view of this, we have selected an intramolecular Diels–Alder reaction of 3,5-hexadienyl acrylate ester (**A**, Fig. 1a). **A** was prepared following the literature.[24,25] The bulk-phase reaction (Fig. 1a) is known to occur in aqueous media catalyzed by indium(III) triflate at an elevated temperature (70 °C).[23] It is reported that the nonpolar solvent cannot drive this reaction.[23] When we performed the reaction both in bulk (Fig. 1b and c) and in microdroplets (Fig. 1d–f) under different conditions,[26] we observed that the reaction in the microdroplet did not yield the desired Diels–Alder product (**B**). Rather, a small amount of

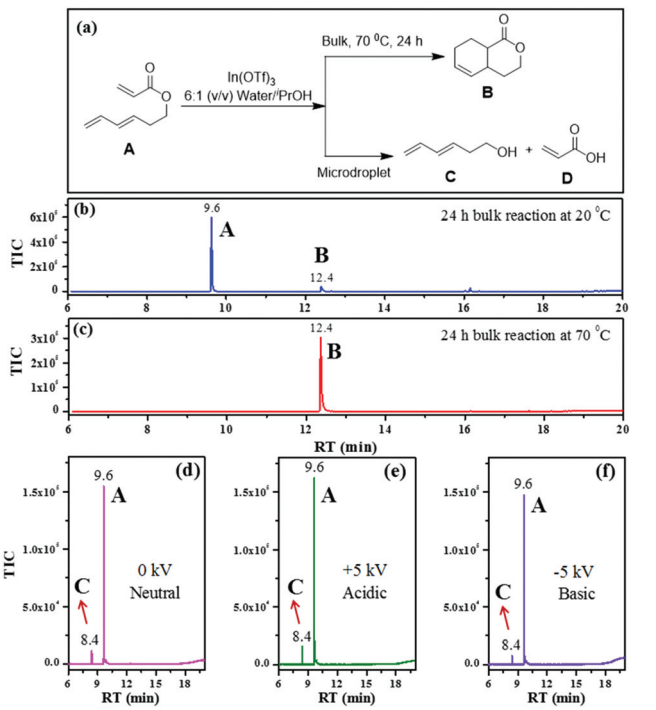

Fig. 1 (a) Schematic presentation of the intramolecular Diels–Alder reaction of 3,5-hexadienyl acrylate catalyzed by indium(III) triflate [$In(OTf)_3$] in the bulk phase consisting of water and isopropanol (^{i}PrOH).[23] The bulk-phase reaction mixture was extracted in diethylether and analyzed by GC-MS after 24 h reaction at (b) 20 °C, and (c) 70 °C. The corresponding microdroplet reaction (off-line) was also studied by GC-MS upon spraying the mixture of reagent and catalyst from the same solvent at (d) 0 kV (pneumatic nebulization), (e) +5 kV electrospray, and (f) −5 kV electrospray. The details of offline microdroplet synthesis at room temperature are reported elsewhere[6] and also briefly described here.[26] The structures of **A** and **B** were characterized by NMR and GC-MS. GC-MS identified the alcohol **C** but not the acid **D**.

hydrolyzed product (hexa-3,5-dien-1-ol) was detected by gas chromatography mass spectrometry (GC-MS) as shown in Fig. 1d–f. The reactant (**A**) remained mostly unreacted. The microdroplet lifetime was also varied by changing the initial droplet size, droplet travelling distance, and droplet evolution by tuning different parameters.[26] However, this did not alter the nature of the product; no Diels–Alder product was detected in all cases. No substrate hydrolysis was observed in microdroplets in the absence of a catalyst (data not shown). Although we observed before that microdroplets can largely circumvent the need for an elevated temperature in a reaction,[3] this Diels–Alder reaction has not been successful in microdroplets produced under ambient conditions. The exact reason for the failure of this reaction in microdroplets is unclear. However, it is apparent that the microdroplet surface, during its short lifetime, does not promote this catalytic Diels–Alder reaction, which is in contrast to the success of the bulk reaction (Fig. 1c) under thermal conditions that overcomes the activation energy barrier. The microdroplet lifetime is limited (on the order of ms) because of rapid evolution (evaporation, Coulomb fission, time before capture, *etc.*). Therefore, any measured acceleration factor (Table 1) is based on this time window (microdroplet lifetime). A very small extent of the Diels–Alder reaction may not be measured during this short reaction time. The present example (Fig. 1) indicates a distinctly different reaction environment in the microdroplet, which, instead of showing marked reaction rate acceleration compared to bulk, shows a completely different route of reaction presumably from the droplet's surface activity. The structural analysis of **A** suggests that the ester functional group, being relatively polar, possibly experiences some surface effect of the microdroplet and therefore undergoes to some extent acid-catalyzed hydrolysis (Fig. 1d–f). On the contrary, the same reagent (**A**) in bulk (Fig. 1b) was not hydrolyzed under similar reaction conditions for prolonged periods of time (24 h). These results once again indicate that the special polar environment of the microdroplet surface should favor some polar reactive reactants for driving the reaction in an accelerated rate, and the nonpolar reaction (*e.g.*, the reaction between the conjugated diene and dienophile in **A**) may not be favored by the polar droplet surface. This fact needs further study to ascertain what kind of reactions could be performed efficiently using the microdroplet as a tiny reaction vessel but caution should be exercised in assuming (1) a reaction in an ESI-generated microdroplet yields the same products as the corresponding reaction in bulk and (2) arbitrary reactions in bulk can be accelerated by carrying them out in microdroplets.

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26 The microdroplet synthesis was performed using a home-built ESI source at 20 μm min^{-1} reagent mixture solution flow with a coaxial sheath gas (nitrogen) flow of 120 psi at different spray voltages (Fig. 1d–f). The microdroplets were allowed to traverse through a grounded glass column bottom sealed with silica gel material from where the product and unreacted starting materials were collected in dichloromethane and analyzed by GC-MS. The droplet lifetime was also allowed to change by varying the column lengths (10 cm and 40 cm), solution flow (5–30 μL), and sheath gas flow (100–150 psi). None of these efforts helped in detecting the desired product **B**. Rather, ester (A) hydrolysis was evident in all cases, similar to Fig. 1d–f.