Microdroplet Chemistry: Difference of Organic Reactions between Bulk Solution and Aqueous Microdroplets

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Abstract

Recent applications of microdroplet reactions are noted as reaction acceleration in confined environments and possible future scale-up synthesis compare to that of bulk phase reactions. Microdroplet reactions overcome the thermodynamic and kinetic challenges in an aqueous solution. Due to the microdroplet's distinctive surface environment, the chemistry in Microdroplets significantly differs from that in the bulk solution.

Keywords: Microdroplet; Noncovalent complexations; Electrostatic potential; Organic reactions

Introduction

Remarkable findings intrigued people in different fields by showing that extremely slow bulk phase reactions can be accelerated dramatically in aqueous microdroplets [1,2]. Not only the rate of the reaction but also the yields of reaction increased due to negative free-energy change which is lower than the value in the bulk phase. Recent experiments have been done by several groups and they validated how microdroplet reactions enable to accelerate organic reactions such as addition reactions [3], condensation reactions [4,5], elimination reactions [2], substitution reactions [2], redox reactions [6], rearrangement reactions [7], and noncovalent complexations [8]. In this mini-review, we show the recent progress about the kinetic and thermodynamic change of organic reactions in aqueous microdroplets, as names as microdroplet chemistry, and its limitation.

To address how reactions in water microdroplets can significantly differ from those in the bulk phase, many experiments have been done and gave clues for the understanding (Table 1). In specific, the reduction of 2,6-dichlorophenolindophenol by the microdroplet fusion method is accelerated by a magnitude of 10^3 [6]. Base-catalyzed Claisen-Schmidt condensation of 1-indanone with electro spray ionization [ESI] is accelerated by a magnitude of 10^4 [4]. And the Pomeranz-Fritsch synthesis of isoquinoline, which is done by using ESI, is also accelerated by the order of 10^6 [7]. These reactions substantiate an increased rate in the microdroplet reaction by many orders of magnitude compared to the extremely slow kinetics in the bulk phase [1,2].

Table 1: Examples of the acceleration of reactions in microdroplets from Ref. [1].

Reaction	Acceleration Factor	Reference
1. Reaction of Girard's reagent T with ketosteroids	$\sim 10^2$	[3]
2. Base catalyzed Claisen-Schmidt condensation of 1-indanone	$\sim 10^4$	[4]
3. Hantzsch synthesis of 1,4-dihydropyridines	$\sim 10^5$	[5]
4. Imine synthesis	~ 45	[17]
5. Reduction of 2,6-dichlorophenolindophenol	$\sim 10^3$	[6]
6. Noncovalent complexation between cytochrome c and maltose	$\sim 10^3$	[8]
7. Pomeranz-Fritsch synthesis of isoquinoline	$>10^6$	[7]
8. Friedlander synthesis of a substituted quinolone	$>10^5$	[7]
9. Combes quinolone synthesis	$>10^3$	[7]

Within the distinctive environment of water microdroplets with different thermodynamic and kinetic properties compared to the bulk phase, an intriguingly plausible biochemical reaction mechanism in aqueous microdroplets were also reported, which might occur prebiotically in the absence of enzymes [9,10]. The abiotic production of sugar phosphates and ribonucleosides naturally does not occur in bulk aqueous solution, because of their thermodynamic hurdle [11]. Within a bulk phase, both phosphorylation and ribosylation of ribose, phosphate and nucleobases are extremely unfavorable, due to condensation of reagents accompanied by the elimination of water [12]. These reactions in bulk phase have an extremely low equilibrium constant [K_{eq}] and a positive free-energy change, which leads to reverse process of hydrolysis of the biopolymer. On the contrary, the reaction in microdroplet provides a negative free-energy change. It substantiates a possible route for the prebiotically plausible formation of sugar phosphates and ribonucleo sides in microdroplets as shown in Figure 1. In the crowded interior of the microdroplets, longer range attractive forces can provide organization of molecules and decrease the organic reaction's Gibbs free energy [13]. This leads favorable change in free energy and acceleration in reaction rate along with high yields. In consequence, although there is lack of evidence, the unique reaction environment by the surface of microdroplets might provide the clue of prebiotic chemical interaction which is significantly related to the possible routes of the origin of life [14]. Because, water-air interfaces on oceans, lakes, aerosols, and cloud and fog droplets can provide reaction environments for the abiotic organic reactions [15,16].
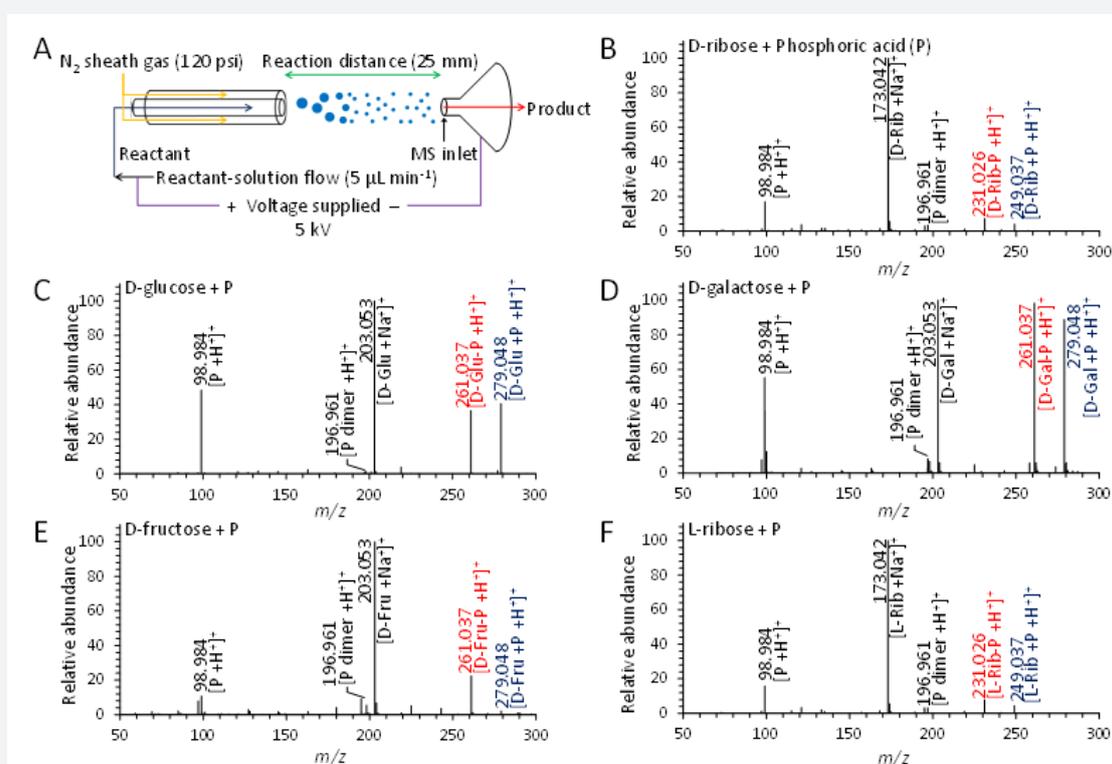

Figure 1: Schematic diagram of electrospray ionization [ESI] method for microdroplet chemistry and the mass spectra of various sugar phosphates produced from water microdroplets including sugar and phosphoric acid precursors from Ref. [10].

The organic reactions in water microdroplets [Microdroplet chemistry] are related to the concentration change of reactants in surface of microdroplets and the distinctive trait of the surface [1,2]. First, the concentration of reactants increases by the evaporation of a solvent on the surface of microdroplets, which makes a reaction acceleration [2]. In chemical reaction, Keq, is a value that never changes. To maintain that value, as the amount of reactants increases, the amount of the products must increase as well. Second, there is an orientation of reactants by the electrostatic potential on the surface of microdroplets, which brings about a decrease of an entropic hurdle in the chemical reaction [17]. At the interface, the characteristics of liqiudare different from in bulk solution. It means that the entropy of water in bulk is higher than at water-air interface and that there is very little chance that the water will react and form products. But, it is different when dealing with the water molecules at the air-liquid interface [9,10]. Near the interface, the water molecules organize and get anisotropic structures. This leads water molecules to gain charges and form an electric field, which affects the reaction rate [18]. That can make multiple parameters that affect the chemical reaction in the microdroplet such as pH, surface charge, reagent confinement, desolvation, contact ion pairing, large electrostatic pressure and molecular orientation on the droplet surface [9,10].

The above observations seem too common related to the kinetic and thermodynamic changes of organic reactions in water microdroplets. The superfast and thermodynamically changed organic reactions are maybe possible to open new chapter of chemistry [2]. At this chapter, we need to more precisely consider if there are some limitations in microdroplet chemistry. As shown before, many researches on acid-or based-catalyzed reactions or the reactants containing polar functional groups proved that the reactions in the microdroplet are accelerated or thermodynamically changed [2-10]. However, there is little information about nonpolar compounds reaction in microdroplets. As a model of non polar organic reaction, the intra molecular Diels-Alder reaction of 3,5-hexadienyl acrylate ester was conducted recently [1]. The bulk phase, When the reaction in the bulk phase was performed with a catalyst of indium [III] triflate, it was reported that the reactants changed to Diels-Alder product at 70ºC.When the reaction is conducted in microdroplets, the expected product is not observed, buthexa-3,5-dien-1-ol was detected. It notes that the interface factor negligibly affects the nonpolar organic reaction because there is little chance of the special polar surface of microdroplets favor nonpolar reactive reagents [1].

Conclusion

We introduce the recent success of microdroplet chemistry in view of the acceleration and thermodynamic preference change of general organic reactions. The reaction mechanisms are not completely understood, there are two main factors for the favorable change of the kinetics and thermodynamics of reactions in microdroplets. Concentration is one factor that attributes to the acceleration of the reaction rate in confined aqueous environments [2]. Because of the surface area of the droplets increases, the area in which droplets can evaporate increases as well compared to that of the bulk solution. This leads to an increase in the concentration of the reactants. To balance the equilibrium, the products increase as the reactants increase, which leads to a higher amount of yields. Second, the natural high surface to volume ratio of microdroplets can generate unique surface characters at the air-water interface [1-8]. As molecules in water droplets approach closer to interface between water and air, their organized water-air environment leads electric field to alter pH, surface charge, and orientation of reagents at surfaces [19,20]. Even though there is a limitation that water microdroplet chemistry is not favorable to nonpolar interaction, the water microdroplet chemistry can lead to facile organic synthesis technique and give the precise knowledge of chemistry in confined environment including biochemical processes in a cell nature [14].

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