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Review

Continuous flow chemistry: New strategies for preparative inorganic chemistry

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ABSTRACT

Uncovering the unique characters of continuous flow chemistry is an important stepping stone in harnessing its power for technological innovation in preparative inorganic chemistry. Compared to the traditional inorganic synthesis under one-pot solution processing conditions and hydrothermal/solvothermal/ionothermal reactions, continuous flow chemistry is a process intensification technology and is advantageous in precisely controlling reaction rate, increasing and scaling up synthesis, and delivering products with maximum yields. This review summarizes the application of continuous flow chemistry in the separation and extraction of inorganic compounds and the synthesis of metal–organic frameworks, polyoxometalates and organometallic compounds.

Contents

1. Introduction

Micro-reaction technology studies the behavior of fluids at the microscopic and mesoscopic scale, which allows for the improvement of synthesis and analysis efficiencies significantly through miniaturization and has garnered remarkable achievements [1] in not only academic research area, but also in industrial applications [2]. This technology has developed dramatically in the fields of organic and pharmaceutical synthesis, analytic chemistry and petrochemical industry, and continues to be a vital application over the past decade. In principle, due to this technology's capability in precisely tuning diffusion, mixing, mass and heat transport,

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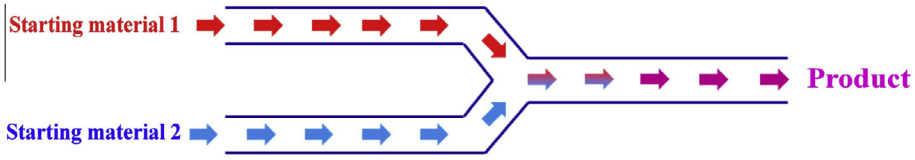

Fig. 1. A representative scheme of flow chemistry.

there is a subsequent improvement in finely controlling reaction rate, increasing and scaling up synthesis, and delivering products with better yields. Primarily, microreaction technology has been integrated with other disciplines – including physics, microprocessing and biological technology – and its application has expanded from separation technology and analytical sciences into different areas, such as natural product syntheses, pharmaceutics, agricultural chemicals, materials, foods, environmental and life sciences and technologies.

Micro-reactor [3], or micro-channel reactor, are miniature reactors with characteristic dimensions that vary between 10 and 300 μm. In general, "micro-reactor" is a generic term for micromixers, microreactors, microheat units, microcontroller (sensors) and other known microchannel devices, and these are often used as continuous flow reactors and are, by definition, dissimilar to batch reactors. "Micro" in this context indicates that the fluid channel at a micrometer scale, and is not specific to the size of the analysis system or the quantity of samples suitable for processing. Importantly, over the past decade, new microreaction methodologies have allowed for breakthroughs in the field of chemical synthesis, which has increased the scale of reaction channels, expanding to the millimeter level due to enlarged process requirements and is now recognized by the more precise term of "continuous flow chemistry" in the chemistry community [4].

In continuous flow chemistry [5], starting materials are pumped into a microreactor at a specific flow rate and the reaction is conducted in a continuously flowing reaction stream (Fig. 1). The method has unique advantages: (i) enhanced control of experimental variables and improved reproducibility; (ii) greater ease in separating target products and by-products, while integrating traditional independent multi-step reactions into a single one-step reaction that is more automated and systematic; (iii) accelerated reaction speeds as reactants can undergo rapid heat/mass transfer. This technology has important implications in green chemistry and laboratory automatization [6,7].

Several excellent reviews have summarized the application of microfluidic flow chemistry techniques. PuigmartÍ-Luis [8] presented the use of microfluidic platform for preparation of crystals, while Cabuil et al. [9] discussed the application of microfluidics in liquid–liquid extraction, synthesis of semiconductors, nanoparticles and self-assembly of advanced materials. Marre and Jensen summarized the recent progress in the field of synthesizing micro and nanostructure with the help of microfluidic technology and they highlighted the importance of supercritical conditions (higher temperatures and pressures) which are unavailable in traditional batch-type reactions [10]. Moreover, Marre et al. also discussed the transferring process from coordination complexes to nanomaterials under flow-type reaction [11]. Ley et al. [12] summarized the production of quantum dots, nanoparticles, polymers and dyes under flow chemistry and continuous processing techniques. A nice review written by Hessel et al. [13] overviewed the recent achievements on the preparation of various metallic nanoparticles (Au, Ag, Pd, Pt, Cu) in continuous flow devices, and also pertinently analysed and discussed the promise of *in situ* formed nanoparticles that could be used as nanocataylsts for organic reactions.

In the field of preparative inorganic chemistry, continuous flow chemistry has enhanced the separation and extraction of inorganic substances, as well as the synthesis of metal–organic frameworks and other inorganic materials, but the potential in inorganic compound preparation has yet to be achieved. This review aims to summarize inorganic compounds that can be successfully obtained by continuous flow chemistry but are difficult to be obtained via traditional methods. As such, this review will not focus on quantum dots, nanoparticles, but instead covers the extraction and separation of inorganic compounds, synthesis of metal–organic frameworks, polyoxometalate clusters and organometallic compounds for the following reasons: (i) extraction is a viable route to purify products in preparative inorganic chemistry and during this process, on-line analysis coupled with a flow reactor, providing a powerful tool in monitoring the reaction; (ii) currently, metal–organic frameworks production is dominated by one-pot solution processing conditions via hydrothermal / solvothermal / ionothermal reactions, which usually suffers from long operation times, low reaction efficiencies, and inconsistent production properties that vary from batch to batch; (iii) polyoxometalate compounds are currently under intense scrutiny due to their structural diversity and applications in catalysis, molecular electronics, and medicine. To date, the majority of these compounds have been obtained by 'one-pot' synthesis, but more recently, continuous flow chemistry has been successfully applied to the synthesis of a series of unprecedented polyoxometalate compounds, demonstrating technological innovation at the academic level. We believe that unraveling unique characteristics of this method is the stepping stone to harnessing its power for technological innovation in preparative inorganic chemistry. Overall, this is a field in which the inorganic/material chemistry community shares a common interest and certainly, it will inspire more researchers to apply this method to their research, either in academic or industrial field.

2. Technical characteristics of flow chemistry

The objective of this review is to provide pertinent, up-to-date information on the use of continuous flow chemistry in inorganic compound and cluster synthesis. Specifically, this technique has attracted widespread attention from a functional material viewpoint, while its application in preparative inorganic chemistry has been exploited to a lesser extent. There are many advantages of flow chemistry, including mixing via diffusion, high surface-area-to-volume ratios, efficient heat/mass transport, superheating to accelerate reaction rate, operating high safety, ability of multi-step synthesis and the scalability features. Jensen et al. [6] and Noël et al. [14] have summarized those striking characters and readers who are interested in the chemical engineering principle could refer to those specialized reviews.

2.1. Mixing via diffusion

Mixing of reagents is often considered as the first factor that influences the results of a reaction. Generally speaking, viscous forces prevail over inertial forces (i.e., $Re < 1$), while mixing would depend on diffusion among fluids without the help of agitator. Reagents reach a chaotic, non-repetitive flow of mixing state by