Continuous Photoflow Synthesis of Precision Polymers

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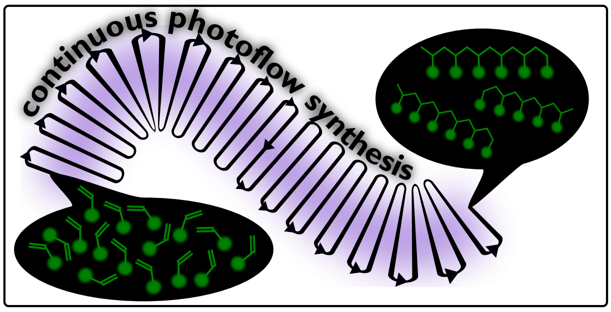
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Continuous Photoflow Synthesis of Precision Polymers

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Precision polymer design in continuous photoflow reactor is a young, yet rapidly growing research field. By switching from batch to flow processing, polymerizations can be carried out with unmatched efficiency under mild reaction conditions, while concommitantly providing conditions for simple scale up of reactions. Specifically the reversible deactivation radical polymerization (RDRP) techniques have gained significant interest in this respect within the past one to two years. The different photoRDRP methods are herein compared and the underlying principles of the advantage of carrying polymerization out under photoflow conditions are elucidated. Further, the yet unexplored potential of these technqiues is identified and discussed towards future devlopment.

Photoflow Chemistry

Controlled polymerization techniques, starting from anionic polymerization to the plethora of controlled radical polymerization techniques (referred to as reversible deactivation radical polymerization, RDRP) are without doubt the gold standard of contemporary polymer synthesis towards advanced materials. The possibilities in macromolecular design are virtually endless – especially in combination with modular click chemistry[1] approaches – and almost any macromolecular architecture can nowadays be targeted in one way or another. While such tailor-made materials open the window to a realm of materials with unprecedented biological, physical, thermal and mechanical properties, this raises as well the need for efficient pathways to synthesize these compounds in significant amounts. In research, highly precise polymer materials are often only obtained on the milligram scale, a hurdle that must be overcome in order to give access to material testing and ultimately to application.

Flow techniques take hereby a prominent role and in recent years much focus was spend not only on bulk polymer and polymer particle synthesis,[2] but also to precision polymerization techniques.[3] As could be shown, small diameter flow reactors allow not only for simple scale up of such polymerizations, but also allow to synthesize materials with increased precision and hence advanced properties due to the more stable reaction conditions and improved isothermicity of the reactions.[4] To date, practically all relevant polymerization techniques have been translated to micro- or mesoflow processing, including anionic and cationic polymerization,[5, 6] reversible addition fragmentation radical chain transfer polymerization (RAFT),[7] atom transfer radical polymerization,[8, 9] single-electron transfer living radical polymerization (SET-LRP),[10] nitroxide-mediated polymerization (NMP)[11] or classical azide-alkyne cycloadditions[12] to name the most relevant synthesis techniques.

A development that occurred at the same time in the field of polymer design is a renaissance of photo-induced reactions. Within only a few years, photo-induced reaction routes for all above mentioned synthesis techniques have been developed and optimized. Research activities in the field are on a steep rise and constantly new variations of photoactivated RDRP methods are published. Especially the ability to choose between different activator/sensitizer systems gives room for broad and efficient protocol optimizations.[13-18] Photopolymerizations feature less side product formation and give access to fast, yet simple reaction protocols. As advantageous as these reactions are, they also feature a significant disadvantage; inherently, photo-induced reactions are difficult to scale up since increasing reactor volumes lead to intensity gradients in the reactors and hence loss of reaction efficiency. Only few options exist to overcome this problem.

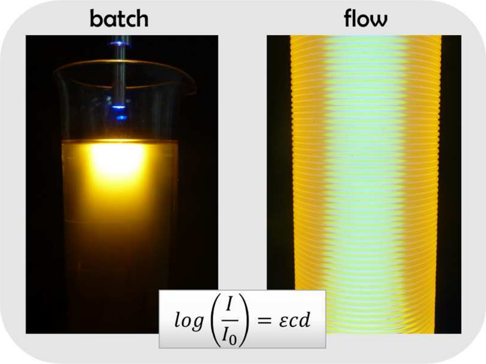

Figure 1 Light intensity profile in a batch reactor (left) and a tubular flow reactor (right)

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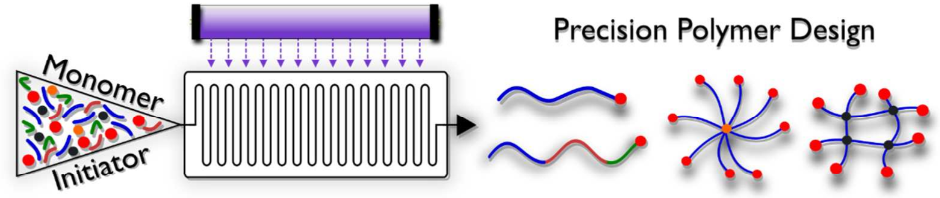

Figure 2 General scheme displaying precison polymer synthesis in photoflow reactors.

Light gradients occur according to Beer- Lambert's law, which correlates decreasing light intensity with increasing optical path lengths. Often, this effect is underestimated, but in fact even with moderate extinction coefficients, no significant light penetration is achieved in a batch reactor above the length of tens of millimeters. A visualization of the light gradient effect is shown in Figure 1, which compares the light intensity profile in a batch reactor with a typical flow reactor (in which a small diameter PFA tubing is wrapped around a light source).[19-22] Both reactors are filled with a solution of poly(3-hexylthiophene), a fluorescent polymer. As can easily be seen, all light is absorbed in the batch reactor in the top layers, even though a 100 W UV lamp was used for irradiation. Strong light gradients exist and any chemical reaction will only occur at the reactor surface. In contrast, the flow reactor – due to its much smaller average diameter, is fully illuminated and practically at no position intensity gradients are observed.

The 'Beer-Lambert penalty' can in batch not be fully overcome. Flow reactors deliver a very convenient, and at the same time very economical way to scale photoreactions up. Due to the much better light efficiency of photoflow reactors, reactions are also significantly speed up, in some cases from days of reaction times to few minutes.[19] Also, formation of degradation products can be avoided as total illumination times are shorter, and lower light intensities can be used. A good example for such scale up from the polymer world is the [2+2] cycloaddition reaction between polymers bearing maleimide endgroups and functionalized alkenes. Such reaction proceeds on the timescale of tens of hours in conventional batch reactors, but is efficiently carried out within 1 min under photoflow processing.[23, 24] While batch reactions are typically performed on milligrams of materials, even in small mesoscale flow reactors up to hundreds of grams can be synthesized with ease. Also, less side products are found in the crude, and the reaction becomes significantly more efficient, as the large excess of ene component required in batch is reduced to almost equimolar ratios in flow.

Photoflow reactors are thus the ideal solution for the above sketched problem of upscaling photoRDRPs. Further, they still retain the classical advantages of flow reactors for precision polymer synthesis (stable reaction conditions, scalability, reliability and reproducibility) and combine them with the advantages of photo-induced chemical transformations such as mild reaction conditions and energy saving. In other words, *the combination of flow technology with photo-induced polymer reactions is a perfect couple*. The very high potential of the combination has already been exploited in first proof-of-concept studies. This minireview summarizes these advances to highlight the achievable efficiency gain that is reached, and gives an outlook to future potentials and endeavours in this rapidly developing field.

photoRDRP flow methods

Controlled polymerization techniques generally give access to polymer materials with defined length, endgroup functionality and narrow dispersity. Polymers are 'reactivatable', and hence allow for block copolymer formation. Combined with advanced initiator and control agent design, macromolecular architectures ranging from rather simple linear structures to brush or star-shaped complex dendritic materials can be produced (**Figure 2**). By adjusting the solubility of the various blocks incorporated in the macromolecules, so called 'smart materials' can be obtained, which are able to react to outer stimuli such as pH, temperature, light or an electrical current. Photo-induced reaction modes exist for practically all reversible deactivation radical polymerization methodologies, but are to date not yet exploited to full potential. These RDRP protocols are often very robust and can be carried out under less stringent reaction conditions compared to other living polymerizations, e.g. anionic polymerization. Generally, two different types of RDRP exist. Control over the polymerization reactions can be exerted via complex degenerative chain transfer equilibria in which chain propagation probability is evenly distributed over all present polymer chains, or via reversible termination reactions, which work via a reduction of free-radical concentrations during polymerization. Both types are discussed in the following.

Photo-induced reversible termination methods

In reversible termination polymerization methods the propagating radicals are terminated reversibly in an efficient control equilibrium. The majority of chains are at any instance in the dormant state and radical concentration are largely reduced, avoiding radical termination and hence inducing living character. The most known techniques are transition metal-mediated polymerizations (ATRP and SET-LRP) and NMP (for mechanisms the reader is referred to the cited literature). Metal-mediated photo-initiated polymerizations employing cobalt, copper and iridium for different monomers are reported in literature. For all systems a significant rate increase from batch to flow reactors is observed (**Table 1**). So far, the largest increase in polymerization rate was observed for Co-mediated polymerization of vinyl acetate from 30 to 1 hour, nicely demonstrating the flow advantage. Further, batch Co-mediated reactions are unstable and yield significant side products. The constant reaction conditions in flow improved

Table 1 Overview over the most common photo-initiated RDRPs in batch and flow reactors. (M_n = number average molecular weight, M_w = weight average molecular weight, *Đ = dispersity*)

#	Method	Reactor	Monomer	Reaction Time [min]	Conv. [%]	M_n [g mol^{-1}]	Đ (M_w/M_n)
1[25]	Co-mediated	batch	vinyl acetate	1 800	26	18 500	1.33
2[25]	Co-mediated	flow	vinyl acetate	60	30	14 200	1.28
3[13]	Cu-mediated	batch	methyl acrylate	90	95	4 500	1.05
4[26]	Cu-mediated	flow	methyl acrylate	20	79	3 100	1.10
5[27]	Cu-mediated	batch	methyl methacrylate	420	88	2 900	1.23
6[27]	Cu-mediated	flow	methyl methacrylate	60	48	3 100	1.24
7[28]	Ir-mediated	batch	methyl methacrylate	1 260	80	6 300	1.19
8[29]	Ir-mediated	flow	methyl methacrylate	220	42	5 400	1.21
9[30]	photoRAFT	batch	*n*-butyl acrylate	3 000	46	20 700	1.12
10[31]	photoRAFT	flow	*tert*-butyl acrylate	60	81	29 800	1.21
13[32]	NMP2	batch	methyl methacrylate	40	58	20 100	1.36

the yield quality and no side products were found.[25] Also Ir-catalysed systems show faster reactions in photoflow compared to batch reactions. However, the increase is not as dramatic as with Co-catalysts. The third reported metal, copper (by far the most widespread system), displays similar advantages with increasing reaction rates (**Table 1**). A direct comparison of Ir- and Cu-mediated polymerizations of methyl methacrylate show that copper enables much faster polymerizations, even though the underpinning reaction mechanism is relatively similar. For both metals, however, reaction rates are increased from batch to flow by a factor of roughly 6. Copper leads in comparison to all other metal catalysed systems to the fastest polymerization, allowing for good yields with concomitant high product quality.

For methyl acrylate, 79% conversion is reached within 20 minutes reaction time in a photoflow reactor with good yield quality. Thus, all three systems display large efficiency gains. The absolute rate obviously also depends on the chosen light source. Yet, as in the above discussed reports similar lamps were employed, the conclusion can be made that copper is the best photo-mediator, at least when polymerizing (meth)acrylate monomers. Still, it needs to be noted that not only the rate increase is of significance. As mentioned above, flow processing gives access to significant amounts of products, while batch processing usually does not yield much more than products on the lower gram scale. The third reversible termination method, NMP, has not been carried out in a photoflow reactor yet. Nevertheless, NMP2 (nitroxide-mediated photopolymerization) exhibits by far the fastest polymerization rate in batch. It is hence a matter of priority to study also this method under photoflow conditions.

Photo-induced degenerative transfer methods

The best known degenerative transfer RDRP is RAFT polymerization. RAFT is very versatile and features the advantage that it is driven by conventional radical initiators, and as such is inherently photoactivatable under any condition (unlike reversible termination, where specific reaction conditions need to be established). RAFT is controlled by di- or trithiocarbonyl endgroups. Until today, research on RAFT was mainly focused on thermal initiated reactions in batch[33] as well as in flow reactors.[34] However, photoinitiated RAFT is long known. [30, 35, 36] Consequently, several methods exist to drive RAFT polymerization by use of classical initiators or via use of photoelectron transfer reactions (PET-RAFT).[37] In here, however, we refer to photoRAFT as technique in which the RAFT agent itself absorbs UV light and triggers polymerization, thus in absence of any photoinitiator system. Recently, Chen and Johnson translated such iniferter reaction[38] from batch to a flow processes.[31] Also here, a dramatic increase in reaction rate for acrylate polymerization (see **Table 1**) is observed, without loss of control over the reaction. Compared to the metal-mediated methods the photoRAFT process so far allowed for synthesis of the largest molecular weights. While for the photoRAFT process molar masses up to 100 000 g mol^{-1} are reported[31] for Cu and Ir only lower masses up to 10 000 g mol^{-1} are reported, [26, 29] hinting at some limitations of the reversible termination type reactions, even though further research is probably required to confirm this difference. Overall, photoRAFT is complex, and also here a distinct need is identified for further detailed studies. PET-RAFT, or photoinitiator-driven RAFT may be as favourable, yet, no data is available for such systems (even in batch only limited information is yet available) and their potential remains currently unexplored.

Conclusion and future outlook

photoRDRP has only recently received significant attention, even in classical batch chemistry. The interest in these methods is rapidly growing, owing to the high efficiencies that can be achieved with ease. As described above, the reaction efficiencies can be further significantly increased when switching to photoflow processes. Photoflow offers additionally the engineering advantage that products can be synthesized in significant amounts without the requirement of expensive equipment. All above described reactions can be carried out in simple tubular reactors consisting only of a light source, translucent tubing and a HPLC pump. Reaction mixtures can be kept in dark before injection, thus mixers are often not even required.

With the eminent advantages of photoflow it may be speculated that most laboratories will in future switch (or extend) to flow processing. This not only due to the reasons above, but also because flow offers general benefits to precision polymer design. First studies are already carried out in which complex macromolecular architectures such as star, brush or cyclic polymers are also targeted. Further, flow processes can be conveniently combined with (dark) thermal reactions, thus allowing for sequential modification. Also λ-orthogonal reactions may in future come in the focus of photoflow material design, expanding the tool box from RDRP also to the realm of photo*click* reactions.[39]

The combination of photoRDRP, photoclick and thermal polymer modification reactions (in conjunction with in-line purification) will give access to highly complex material synthesis virtually in one-step procedures. The polymer chemistry community – outside classical polymer reaction engineering – is only at the beginning of implementing flow techniques to the synthesis portfolio. Photoflow, itself even more so an infant research topic in the polymer community, will give further boost to flow adoption due to its striking benefits. With certainty, the above described data are only the beginning of a rapid development, and the full potential of photoflow precision polymer material design and synthesis will soon fully unfold.

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