

Challenges and Opportunities of Precision Polymer Chemistry

Since Hermann Staudinger coined the revolutionary concept of macromolecules in 1920, synthetic polymers have served as a major game changer to our society and become indispensable in our daily lives. Unlike biomacromolecules (*e.g.*, DNA and proteins) possessing precise molar masses/chain sequences/topologies and specific biological functions, synthetic polymers are abiotic materials characterized by broad chain length distributions and undefined sequences. To bridge the gap between natural and synthetic polymers, the biomimetic synthesis of polymers with precise chain length, sequences and topologies has been long pursued and yet unmet in polymer science. Notably, Prof. Staudinger had dedicated his career to establish the connection between life science and polymer science, yet this formidable challenge has been far less solved even after a century. In recent years, precision polymer chemistry has gradually evolved into an important topic. Here I would like to share my personal thoughts on this rapidly developing field of precision polymer chemistry, mainly for junior polymer researchers and graduate students.

Function-oriented polymer chemistry is not sufficient to serve as a major driving force. It is natural and quite popular to integrate and explore multiple functions into polymeric structures. Although potential applications of these polymers have been successfully demonstrated, their potentials in real-life applications can be severely hampered by their complex designs and tedious synthetic procedures. Moreover, although many functions could be integrated and examined, the same functions can be realized by many other different types of materials, and the indispensability of specific polymeric materials is rarely demonstrated. Note that there is no best function but only better function. Furthermore, multi-functional integration could lead to the trade-off among different functions and does not meet practical application circumstances.

Returning to basic materials, simple designs, and asking original questions. Instead of integrating increasingly complex functions, many fundamental questions in precision polymer chemistry have remained to be addressed. For example, how does chain length dispersity affect aggregation state microstructures and functions? Towards this end, there are increasing demands to synthesize polymers with precise primary structures such as polyethers, polyesters, polypeptides, and polyolefins. For example, poly(ethylene glycol) (PEG) derivatives are widely used in clinical drug formulations including micellar and liposomal nanocarriers, lipid nanoparticles (LNPs), and pegylated proteins/enzymes/drugs. Precise versions of these important polymers not only provide an excellent platform to elucidate the correlation between chain

length/dispersity/topology and biological functions, they might also revolutionize the drug delivery field and make a clear distinction among polymer chemists, pharmaceutical formulation expert, and biomaterial scientists. On the other hand, given that biomacromolecules such as DNA and proteins have precise chain lengths/sequences and homogeneous chiral centers with intricate higher-order structures, the fabrication of synthetic precision polymers with primary and higher order hierarchical structures can likely bridge the gap between materials and life sciences. Research along this direction might shed light on some original questions including the origin of biomolecular homochirality in all living organisms, artificial cells and life, and sustainability of human society on earth and other terrestrial planets.

Precision polymer chemistry must involve more sophisticated characterization tools. To enable the efficient synthesis of precision polymers, both scalable synthetic methods and new separation procedures are highly desirable. Conventional procedures such as precipitation and fractionation and (flash) column chromatography cannot serve as reliable methods to obtain precision polymers from dispersed precursors. Instead, recycling preparative gel permeation chromatography (GPC) and supercritical fluid extraction (SFE) techniques provide feasible means to render precision discrete polymers. More importantly, conventional techniques used to measure the molar mass of synthetic polymers, such as GPC, NMR, osmotic pressure, and analytical ultracentrifugation, cannot unambiguously characterize precision polymers, as they just report values of statistical average. In contrast, mass spectrometry (MS) techniques, such as MALDI-TOF MS and ESI-MS either working alone or coupled with chromatographic techniques (HPLC, UPLC, LCCC, capillary electrophoresis, *etc.*), are highly powerful as they could resolve molar masses on single chain entities. Various scattering techniques including small-angle laser light, X-ray and neutron scattering, high resolution cryo-electron microscopy, and single-molecule spectroscopy and imaging techniques could be used in combination. In addition to precise chain length and sequences, the sequence decoding of precision polymers represents another key challenge. Although well-established protocols for sequence reading of nucleic acids and proteins have been developed, they are, unfortunately, not suitable for the analysis of synthetic precision polymers.

A polymer chemistry project that is predictable might imply less scientific significance. Currently, it is not an impossible task to synthesize various polymers and integrate versatile functions into synthetic polymers using the knowledge from established literature reports, but we

should be prudent with these intuitive outcomes and not be overly optimistic with these “rational” designs. Note that important breakthroughs in chemical sciences have generally not been achieved by “rational designs” but by serendipity. If a polymer chemistry project can be completely predesigned and conducted without any unexpected results, it might suggest insignificant advances. Therefore, special attention should be given to unexpected results and uncommon and counterintuitive phenomena, which are the origins of new knowledge creation.

Precision polymer chemistry must contribute to high added-value products and has to solve practical challenges facing the human society. Our ongoing projects show that precision polymers enable the fabrication of single-component photoresists (possibly for EUV applications), avoid the introduction of photoacids, and thus preclude the adverse influence of proton diffusion on resolution. Another intriguing progress reveals that the emergence of precision PEG derivatives provides a feasible solution to alleviate anaphylactic reactions by lowering the production of anti-PEG antibodies, which thus extends blood circulation half-lives and improves biodistributions for liposomal and LNP nanocarriers. Moreover, recent studies have demonstrated that precision polymers, as compared to their chain-disperse counterparts, exhibit distinct physicochemical properties such as crystallinity, solubility, and degradability. Without a doubt, precision polymer chemistry not only provides excellent opportunities to unify polymer chemists and physicists as well as materials scientists with multidisciplinary background, but also shows great promises in biomaterials, environmental, and energy sciences. This can only be limited by our imagination and

depth of thoughts, the desire for waiting that flash of insights, the capability of capturing experimental abnormalities, the grasping of background knowledge and interdisciplinary (apparently unrelated) progresses, the courage to resist from familiar (maybe less promising and challenging) research topics (including those from PhD and postdoc studies), and most importantly, our patience of doing things slowly, carefully, and nicely.



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Notes

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