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Online Mass Spectrometric Characterization of Oligomeric Products in High-Pressure Liquid-Phase Lignin Depolymerization Reactions

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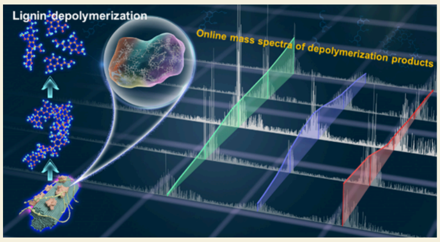

ABSTRACT: Lignin depolymerization involves complex reactions that occur in heterogeneous environments, leading to the formation of a wide range of products with diverse molecular structures. The complexity of these products arises from the different bond strengths and locations within the lignin polymer, which makes it difficult to fully understand the reaction pathways. Conventional analytical techniques often fall short of providing a clear and comprehensive picture of the reaction mechanism. This highlights the need for more advanced methods that can offer real-time, in situ analysis to probe product evolutions and unravel the detailed mechanisms of lignin depolymerization. Herein, we present a concise perspective of the recent developments in online mass spectrometry, particularly its applications in probing heavy oligomeric products formed during lignindepolymerization. After introducing the current analytical technologies and analytical challenges, we focus on the development of online mass spectrometric method, especially those combined with batch and flow-through reactors, for the real-time characterization of lignin depolymerization products. Several key case studies are highlighted. Finally, we discuss the potential opportunities and remaining challenges in this field.

KEYWORDS: *Mass spectrometry, online analysis, lignin, heterogeneous reaction, oligomers*

■ INTRODUCTION

Global climate change and energy shortages have driven the search for the next generation of energy sources and chemical feedstocks to replace fossil fuels (coal, oil, and natural gas).[1] Plant-based biomass, which is the fourth largest energy source on Earth after coal, oil, and natural gas, has emerged as one of the most widely studied and promising renewable energy options in recent years.[2−4] Lignocellulose is primarily composed of three interconnected components-- cellulose, hemicellulose, and lignins[5] -- of which lignin, as a major source of renewable aromatic compounds, holds substantial potential for producing valuable chemicals and fuels.[5−7] Therefore, converting biomass and its byproducts (such as black liquor and wood chips) into value-added chemicals is of great significance in addressing environmental challenges and resource scarcity.[8−10]

The conversion of biomass, particularly lignin, largely relies on thermochemical and catalytic methods, although some processes can be achieved through bioengineering.[11] Generally, these reactions can be categorized by the reaction medium into pyrolysis and liquefaction.[12,13] Pyrolysis and catalytic pyrolysis are widely employed methods known for their advantages, including feasibility of large-scale continuous production and simple product separation.[14−20] However, pyrolysis generally requires high temperatures (≥400 °C), resulting in significant energy consumption and the need for precise control over heating rates and atmospheric conditions.[21] In contrast, biomass liquefaction occurs in a liquid medium under milder conditions, allowing production at lower reaction temperatures (≤300 °C).[22,23] Biomass liquefaction reactions are often conducted in batch reactors or flow reactors, with batch reactors suitable for batch production and flow reactors enabling semi-continuous production.[24−28] These processes typically involve heterogeneous catalytic reactions, such as reductive catalytic fractionation (RCF) and direct hydrogenolysis, where a solid catalyst interacts with the lignin substrate in a liquid-phase environment. Table 1 provides some typical examples of RCF reactions of biomass feedstocks with batch and flow-through reactors, all of which involve elevated temperatures, high pressures, and heterogeneous catalysts. While many studies show high selectivity and yields using model compounds, applying these methods to more structurally complex lignin feedstocks still suffers from low conversion efficiency and low selectivity for target products.

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Table 1. Typical Studies of Biomass Conversion Using RCF Method

Feedstocks	Reactor	T (°C)	H_2 (MPa)	Catalysts
Beech[29]	Batch	200	4	Ru/C
Birch[30]	Batch	250	3	Ru/C
Birch, poplar, pine, oak[31]	Batch	180	3	Pd/C
Klason lignin[32]	Batch	250	4	Pd/C, Ru/C
Birch[25]	Batch	250	3	Ni/C
Poplar[26]	Flow-through	190	6	Ni/C
Poplar[33]	Flow-through	190	6	Ni/C
Birch[34]	Batch	250	4	Ru/C
Poplar[28]	Flow-through	190	6	Ni/C
Black locust bark and wood[35]	Batch	250	4	Ru/C
Beech[36]	Batch	250	1	Ru/C
Poplar[37]	Batch	185	0.1	Ru/C
Pine[38]	Batch	235	3	Pd/C

Since lignin depolymerization involves a series of intricate chemical transformations, including ether bond cleavage, intermediate hydrogenation, and subsequent reactions to generate valuable chemicals, a comprehensive understanding of these mechanisms is essential. Such knowledge will help researchers design more effective catalytic systems and optimize reaction conditions, improving both product yield and selectivity.

Experimentally detecting and analyzing the distribution and evolution of products in such heterogeneous reactions is crucial for understanding the underlying mechanisms. In batch reactors, the “one-pot” nature and the long time-averaging inherent to reactions make it challenging to characterize lignin intermediates.[26] Monitoring reaction evolution in a batch system typically requires cooling the reactor and opening it for sample collection, which can disrupt the process.[4] In contrast, flow systems offer the advantages of collecting time-resolved data during lignin conversion, enabling the separation of solvolysis and hydrogenolysis steps both temporally and spatially. Even with flow systems, traditional product analysis is often conducted offline, necessitating sample pretreatment.[39,40] Complex pretreatment methods such as filtration, rotary evaporation, and derivatization often expose samples to moisture and air, while subsequent chromatographic separation further exacerbates analysis delays, leading to the degradation of reactive intermediates.[41]

Recently, the integration of mass spectrometry (MS) with reactors has emerged as a powerful tool for studying lignin depolymerization under high-pressure liquid-phase conditions. These advanced methodologies combine the reactor with the ionization source of the mass spectrometer, thereby not only eliminating the need for extensive sample pretreatment but also significantly reducing the duration of the sampling process. This integration enables real-time, online measurement of various polymeric products and has proven instrumental in enhancing the efficiency and accuracy of analyzing the complex reactions involved in lignin depolymerization. In this perspective, we present a concise overview of current analytical technologies and the associated challenges, with a particular focus on the development and application of online mass spectrometric methods--especially those integrated with batch and flow-through reactors-- for the real-time characterization of lignin depolymerization products. We highlight several key examples that demonstrate the effectiveness of these approaches.

CURRENT ANALYTICS AND ANALYTICAL CHALLENGES

Accurately characterizing lignin depolymerization products is essential for optimizing biomass conversion processes.[42,43] In high-pressure batch reactors, standard procedures typically involve rapidly cooling the reactor at specific time intervals, followed by opening it to recover products and catalysts.[44,45] Liquid-phase products are then separated from the solid catalysts through filtration or centrifugation. In aqueous systems, organic solvents are often employed for extraction.

Gas chromatography (GC), especially when coupled with flame ionization detection (GC-FID) and MS (GC-MS), remains a foundational tool in analyzing biomass-derived products. GC-FID offers exceptional quantification capabilities, while its integration with MS provides valuable qualitative insights, making GC-MS indispensable in biomass research. However, the utility of GC is inherently limited to volatile, low molecular-weight compounds, making it challenging to detect high boiling-point or thermally unstable products (such as oligomers and oxygen-rich monomers) resulting from lignin depolymerization. To extend the applicability of GC-MS, derivatization techniques, such as silylation, have been developed to increase the volatility and thermal stability of dimers and trimers. Notable studies by Anderson, Sels, and Van den Bosch have employed derivatization-GC-MS to analyze lignin-derived dimers.[26,28,46] Additionally, researchers such as van Geem and Sels have utilized comprehensive two-dimensional gas chromatography (GC × GC-FID/MS) with derivatization and high-temperature-resistant columns, successfully identifying and semi-quantifying various dimeric and trimeric products from the RCF of softwood lignin.[38]

Despite these advancements, the qualitative capabilities of GC-MS are limited by the significant loss of active species information. The complexity of lignin depolymerization products necessitates extensive sample preparation, including exposure to air, filtration, and repeated solvent extractions, which can lead to the degradation of short-lived or oxygen/moisture-sensitive intermediates. Moreover, the prepared samples must undergo high-temperature volatilization before entering the GC columns, and prolonged elution times further increase the risk of losing key intermediates or products.

As interest in RCF reactions grows, there has been an increasing focus on analyzing oligomers, which present unique analytical challenges due to their high molecular-weights and high boiling-points. Techniques such as nuclear magnetic resonance (NMR),[46−48] Fourier-transform infrared spectroscopy (FTIR),[49,50] and gel permeation chromatography (GPC) have been employed to characterize these complex products (Figure 1).

Two-dimensional heteronuclear single quantum coherence nuclear magnetic resonance (2D-HSQC NMR) is currently the standard method for structural analysis in lignin conversion studies. This technique provides qualitative and semi-quantitative insights into the various inter-unit linkages within lignin structure. FTIR spectroscopy, widely used for analyzing functional groups in lignin-derived products, can analyze solid samples directly, making it ideal for studying carbonaceous species, including coke-like deposits. GPC, on the other hand,

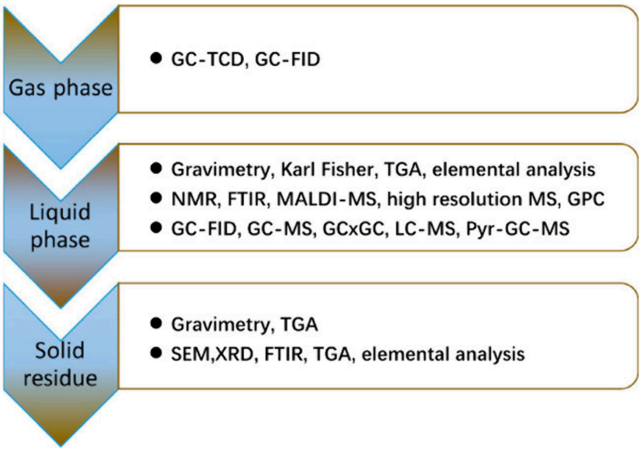

Figure 1. Methods for evaluation of lignin decomposition products and structural motifs in liquid, gas, and solid state. Reprinted from ref 43 with permission from the American Chemical Society, copyright 2016.

estimates the number-average molecular weight (M_n) distribution of lignin polymers based on size exclusion principles, with larger molecules eluting first. However, using polystyrene as a calibration standard may not accurately reflect the properties of lignin polymers due to differences in rigidity and potential steric effects. This discrepancy can introduce significant errors in molecular-weight measurements.

High-performance liquid chromatography (HPLC) coupled with mass spectrometry has also been widely utilized for the analysis of lignin-oil, particularly for oligomers with large molecular-weights (up to 1000 Da).[51−54] Kenttämaa et al. applied this technique for the compositional analysis of organosolv lignin, successfully characterizing oligomers up to tetramers and inferring their structures based on fragmentation patterns via tandem mass spectrometry.[55] Additionally, high-resolution mass spectrometry (HRMS) has enabled the direct injection of liquid samples, providing accurate mass data that can be converted into elemental compositions.[56] This approach provides substantial details and facilitates diverse data representations, such as Kendrick mass defect and van Krevelen (V−K) plots, providing a wealth of information on product types, structures, etc.[57−60] However, most of these studies have been conducted offline, resulting in the loss of significant real-time process information.[61]

While these analytical techniques offer valuable insights into the overall properties of lignin depolymerization products, they are unable to definitively identify the structure and molecular-weight of each individual species within the complex mixture. Furthermore, their reliance on offline analysis precludes real-time monitoring, which is particularly problematic in the study of heterogeneous reactions, where in situ analysis is essential for capturing the true reaction evolution .

Consequently, there is a critical need for the development of in situ analytical techniques capable of operating under harsh conditions of liquid-phase reactions, including high pressures and temperatures. Such techniques must provide real-time data on both the reaction process and the evolving molecule structures. Overcoming these challenges will lead to a more accurate and comprehensive understanding of the catalytic mechanisms involved in lignin depolymerization.

■ ONLINE MS FOR CHARACTERIZATION OF LIGNIN DEPOLYMERIZATION PRODUCTS UNDER HIGH-PRESSURE HETEROGENEOUS CONDITIONS

Online MS without preseparation has usually been applied for real-time analysis, including measurement of product distribution and tracking product evolution over time or as temperature changes. Up to now, state-of-the-art MS techniques have been developed for monitoring the thermal and catalytic pyrolysis of lignin and other types of biomass. By coupling various reactors, such as thermogravimetric (TG), fixed-bed reactors, and fluidized-bed reactors, with photoionization via molecular beam nozzles or heated capillaries, or by incorporating specific furnaces directly into the ionization source, researchers have achieved real-time detection of pyrolysis volatiles.[62,63] This enables real-time observation of characteristic products and intermediates as they evolve.

In gas-phase reactions, molecular mass transfer occurs naturally, making real-time reaction monitoring simpler than in liquid-phase reactions. This fundamental difference has long made it difficult to conduct online MS characterization for lignin conversion reactions under liquid-phase conditions. Recently, significant advancements have been made in applying MS to lignin depolymerization,[64−75] particularly through the integration of online MS techniques that allow real-time monitoring of complex reactions. These approaches have proven invaluable for elucidating the detailed reaction pathways and mechanisms involved in lignin degradation, providing insights that were previously unattainable with traditional offline methodologies.

One of the main advantages of online MS in lignin depolymerization is its ability to provide continuous, real-time analysis of reaction intermediates and products. Unlike conventional methods, which require periodic sampling and subsequent analysis, online MS allows for the direct observation of the reaction as it evolves. Cui et al. have demonstrated how online MS can track key intermediates and products during catalytic hydrotreatment of guaiacol, a typical lignin model compound.[76] An autoclave was directly connected to a time-of-flight (TOF) mass spectrometer via a capillary, with the sample being vaporized in a tiny vaporizer before entering the ionization chamber, as shown in Figure 2.

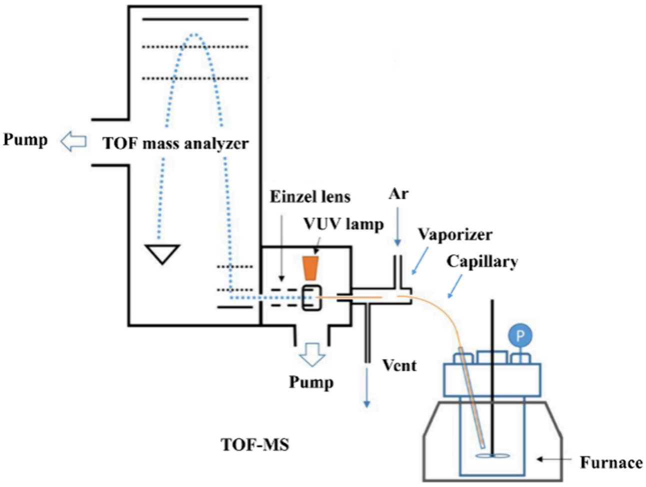

Figure 2. Sketch of the autoclave combined with photoionization TOF mass spectrometer. Reprinted from ref 76 with permission from the American Chemical Society, copyright 2021.

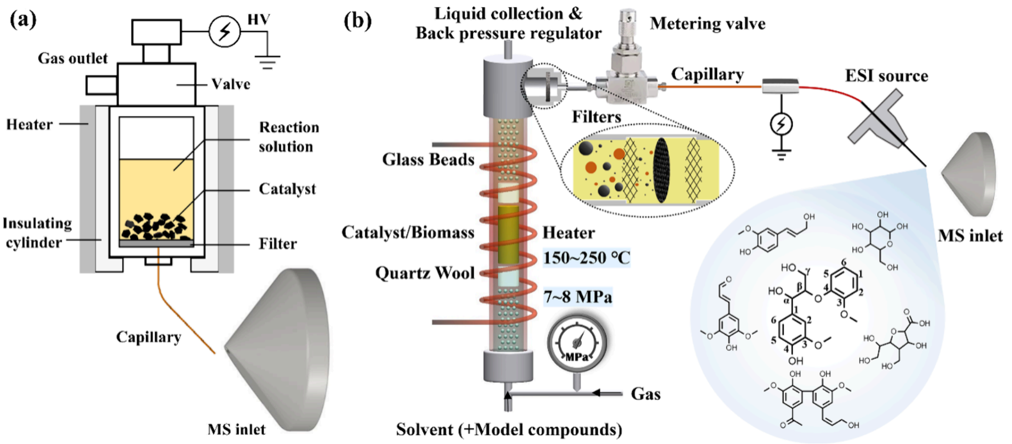

Figure 3. Combination of online HRMS with batch reactor (a) and flow-through reactor (b). Reprinted from refs 77 and 79 with permission from the American Chemical Society, copyright 2021, 2024.

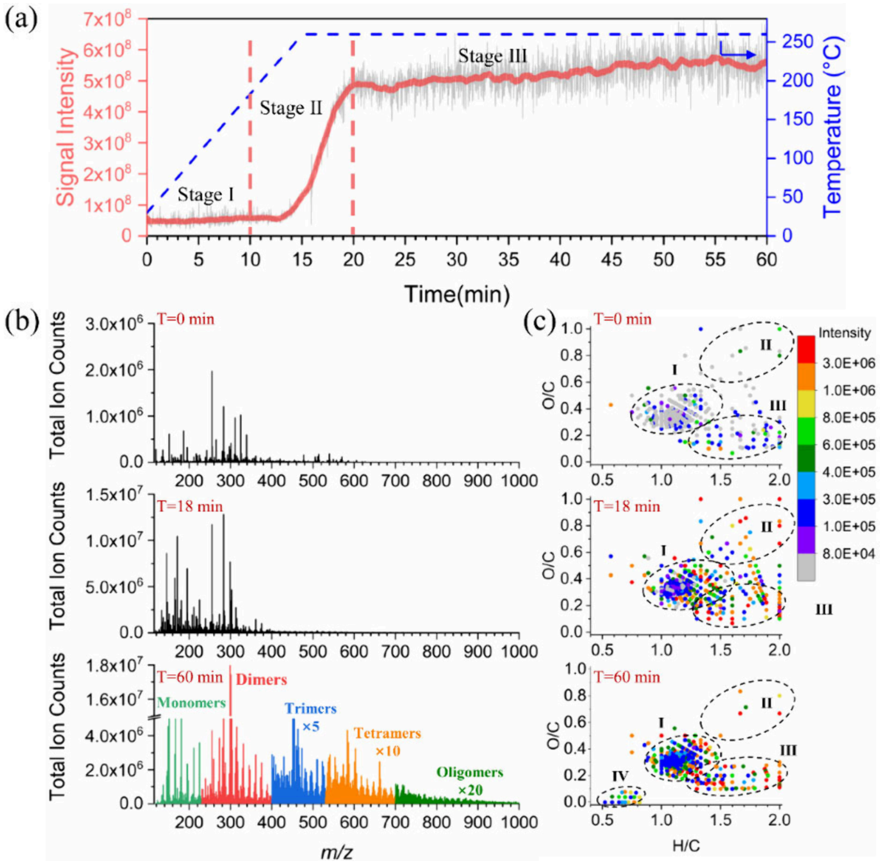

Figure 4. Online mass spectrometric analysis of depolymerization products: (a) TIC evolution with temperature; (b) Mass spectra at t = 0, 18, and 60 min; (c) V−K diagrams from the mass spectra in (b). Reprinted from ref 78 with permission from Elsevier, copyright 2022.

The ionization source utilized a vacuum ultraviolet discharge lamp, emitting photons at 10.6 eV to ensure that most products remained intact during ionization. In such heterogeneous systems, fine catalyst particles can easily cause clogging of capillaries during sampling, leading to interruptions in continuous sampling. To prevent such blockages, a stainless-steel chromatography filter with a pore diameter of 2 μm was installed at the capillary inlet, and a piece of carbon cloth (>99.99% carbon) was used to capture the dispersed catalyst slurry.

Despite the ability of this method to monitor products online, it is inherently limited by sample transfer and vaporization processes, restricting detection mainly to small molecular products. Consequently, the range of detectable products does not significantly differ from that identified by traditional chromatographic offline methods, and measuring heavier components during reactions remains a challenge. A recent advancement has effectively addressed this limitation by integrating the reactor directly with the MS ionization source. This method eliminates the need for traditional sample pretreatment, significantly shortens the time required for

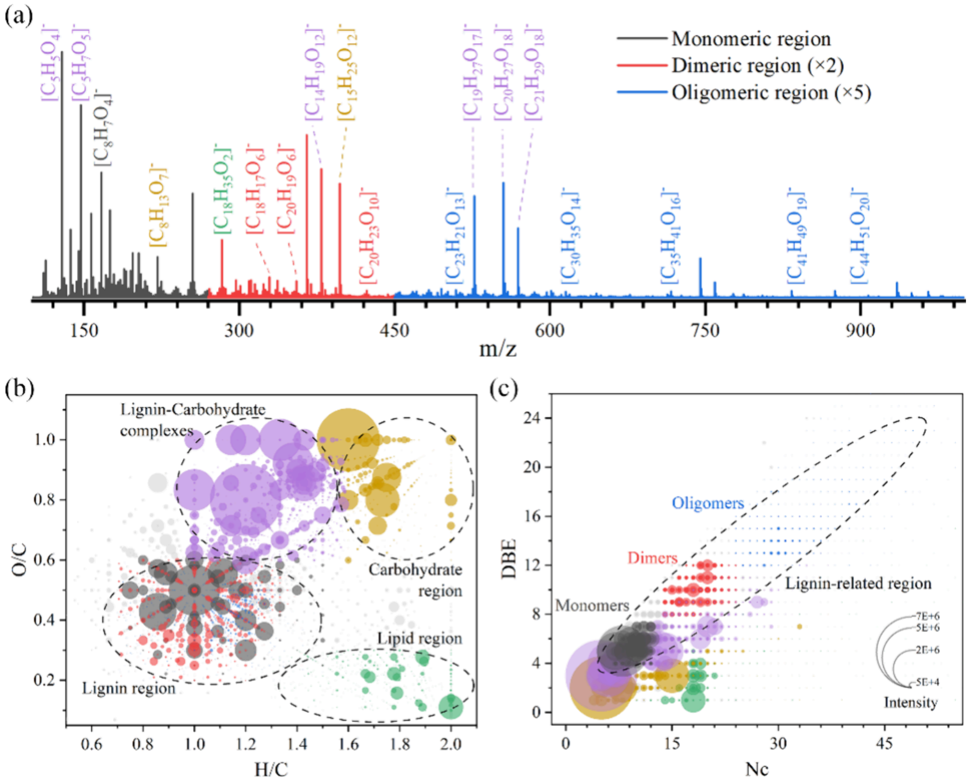

Figure 5. Molecular-level product distribution from birch wood flow-through fractionation: (a) Full mass spectrum recorded 35 min after the reaction started, (b) V−K diagram, and (c) DBE vs N_C diagram from (a). Reprinted from ref 79 with permission from the American Chemical Society, copyright 2024.

sample extraction, and represents a major methodological advancement. By directly coupling HRMS with the reaction system, product evolution within the reactor can be observed with almost no interruption to the ongoing reaction process. This approach has been successfully applied in both batch[77,78] and continuous flow-through reactors.[79,80]

As illustrated in Figure 3a, the reactor-integrated electrospray ionization (ESI) MS system combines a stainless-steel microbatch reactor with a volume of approximately 5 mL. The reactor is housed within an electric heating jacket, and seperated by an alumina insulating cylinder, enabling the reactor to floated at high voltage. A 60 mm long fused silica capillary with an inner diameter of 15 μm is directly attached to the reactor's bottom, serving as both a sampling port and an ESI spray needle, thereby significantly reducing the distance between the reaction zone and the ionization site. Carbon was also placed at the bottom of the reactor to prevent the blockage to the sampling capillary.[77,78]

Figure 3b shows the second case, a continuous flow-through reactor is coupled with HRMS. Here, the reaction takes place in a vertically mounted stainless-steel tube, with the feedstock and/or catalysts securely positioned in the middle by quartz wool and glass beads. The reactor is heated by a copper heating jacket, and the entire system is sealed using VCR or tube fittings, capable of withstanding pressures up to 12 MPa. A tee interface is installed at the reactor outlet for online sampling.[79,80] Thanks to its integration with HRMS and ESI ionization source, this method facilitates the determination of product molecular formulas through precise m/z measurements, and, unlike traditional GC-MS, it is not limited by molecular-weight or boiling point, thereby allowing for the detection of a broader spectrum of high molecular-weight products.[38,46,73,74]

Figure 4 illustrates the evolution of lignin depolymerization products obtained using a batch reactor coupled with high-resolution mass spectrometry. The total ion current (TIC) in the figure reveals three distinct stages corresponding to the progression of lignin depolymerization. Additionally, the mass spectra at different time points highlight changes in product distribution over time. For instance, Figures 4(b-c) present the full scan mass spectra and corresponding V−K diagrams at t = 0, 18, and 60 min. The H/C and O/C ratios in these diagrams differentiate four regions: Region I, the most prominent, corresponds to lignin-derived units, showing significant changes in compound intensity and diversity over time; Region II represents carbohydrates originating from impurities in the commercial lignin; Region III includes residual surfactants, fatty acids, triterpenoids, and lipids; and Region IV contains highly condensed aromatic compounds, which are likely repolymerization products or coke precursors.

Figure 5 illustrates an application where the integration of a flow-through reactor with mass spectrometry enables real-time analysis of biomass degradation, providing superior molecular discrimination compared to traditional methods such as GC, NMR, and GPC. This method is capable of detecting thousands of molecular formulas within a single mass spectrum, capturing a broad range of biomass-related products ranging from monomers to oligomers. The V−K diagram (Figure 5b) highlights distinct regions corresponding to lignin fragments, lignin-carbohydrate complexes, carbohydrates, lipids, fatty acids, and other biomass components. Notably, the majority of products—especially those derived from lignin and hemicellulose—are concentrated in the first three regions, representing the dissolved fragments of these components. Additionally, the DBE versus carbon number (N_C) diagram (Figure 5c) further distinguishes lignin fragments of varying sizes, including structures as large as pentamers, underscoring the superior resolution and detailed compositional analysis enabled by this advanced online HRMS approach.

As mentioned above, the structural analysis of lignin depolymerization products remains a significant challenge, primarily due to the lack of comprehensive spectral libraries for various standard compounds.[81] Tandem mass spectrometry (MS/MS) has played a pivotal role in the structural analysis of lignin depolymerization products.[66] MS/MS techniques can provide valuable information of the molecular structures of products by fragmenting selected ions.[82−84] Dong et al. and colleagues have also used MS/MS to identify the structures of certain lignin-derived compounds.[85] However, this remains insufficient for the comprehensive analysis of lignin's complex products. Very recently, Cui et al. used MS/MS to elucidate the structures of lignin-derived oligomers and monomers, offering insights into their chemical composition and formation mechanisms.[77,78] By combining MS/MS with the reactor-integrated ESI-MS system, researchers also proposed guidelines for identifying the structure of heavy phenolics after or during lignin depolymerization. The dissociation principles for typical linkages such as β-O-4, 5−5, β−β, β-5, and β-1 were established, offering a detailed understanding of their fragmentation behaviors. For instance, β-O-4 dimers dissoaciated via homolysis pathways at 0% dissociation energy via in-source CID, producing distinct fragmentation patterns. 5−5 dimers, characterized by their robust linkages, remained intact due to high bond dissociation enthalpies (BDEs) and intramolecular cyclization, making them challenging to break into monomers. β−β dimers dissociated at the C_β site through homolysis and radical transfer, generating odd-numbered peaks in the MS^2 spectrum. Meanwhile, β-5 and β-1 dimers underwent charge transfer-induced heterolysis, predominantly producing even-numbered peaks. This difference in peak parity helps distinguish β−β dimers from β−5 and β−1 dimers effectively. Using this strategy, a dozen heavy products were identified, and real-time structural evolution was also monitored.[86]

Moreover, online MS has facilitated the investigation of product evolution under varying reaction conditions. By systematically varying parameters such as temperature, pressure, and catalyst composition in real-time while monitoring the resulting changes in product distribution, researchers can explore the effects of different variables on lignin depolymerization with unprecedented precision. Figure 6 shows the evolution of jet fuel precursors during solvolysis of lignin under programmed heating and at a constant 230 °C. The trends observed underscore how the bond strengths and locations within lignin dictate their evolution over temperature and time.[80]

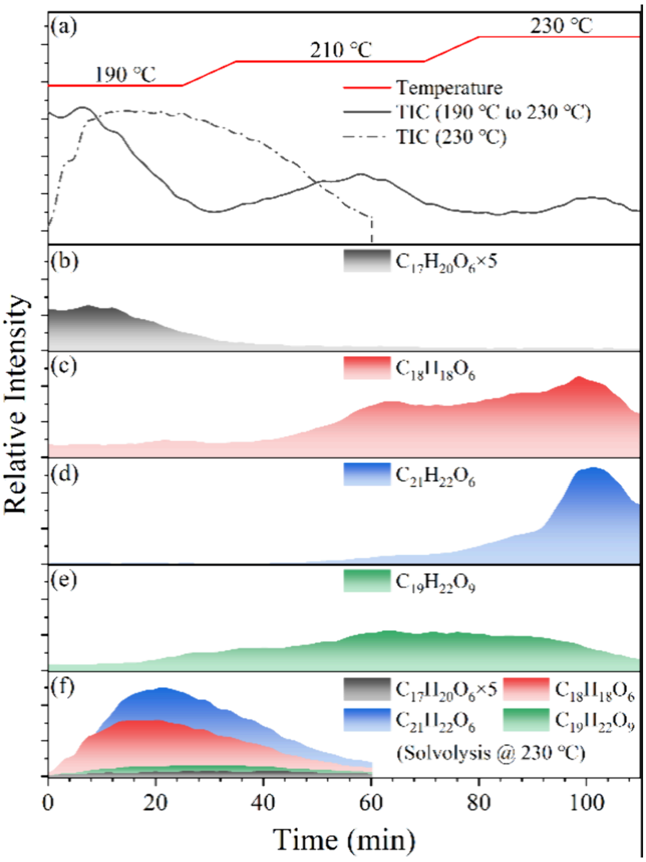

Figure 6. (a) TIC and temperature curves for solvolysis under programmed heating and at a constant 230 °C. (b−e) Real-time evolution of phenolic dimers during programmed heating and (f) solvolysis at 230 °C. Reprinted from ref 80 with permission from the Combustion Institute, copyright 2024.

CONCLUSIONS AND OUTLOOK

This perspective highlights the significant advancements that online MS has introduced to the real-time analysis of complex reaction systems, particularly in lignin depolymerization. One of the challenges in this process lies in the complexity of the resulting products, as lignin's inherently heterogeneous structure, comprising various interunit linkages with differing bond strengths and positions, gives rise to a wide array of reaction products ranging from monomers to oligomers with diverse chemical properties. The capability of online MS to record real-time data on these products is crucial for elucidating depolymerization pathways and identifying key intermediates that may serve as markers for specific reaction stages. Nevertheless, the structural complexity of the product mixture often complicates the precise assignment of structures to all detected species, particularly for heavier oligomers. To address this, MS/MS techniques have been employed to obtain more detailed structural information, enabling the identification of specific functional groups and linkage types within lignin fragments by analyzing ion fragmentation patterns.

Despite these advancements, significant challenges remain in the application of online MS for lignin analysis. For instance, fluctuations in reactor pressure during heating can destabilize the ESI process, leading to variations in the MS signal. To mitigate these issues, future research could explore the use of gold-coated capillaries to enhance electrospray consistency, implement real-time pressure monitoring for signal normalization, and select appropriate internal standards to improve the reliability and quantitative capabilities of in situ MS analysis. Furthermore, integrating photoionization techniques with ESI could broaden the detection capability of online MS, allowing it to analyze both polar and nonpolar compounds, thereby providing a more comprehensive analysis of the mixture analytes.

Moreover, the emergence of machine learning and artificial intelligence (AI) offers promising solutions to the challenges posed by product complexity in lignin depolymerization. These technologies can analyze the vast data sets generated by online MS, identifying patterns and correlations that might not be immediately apparent through traditional methods. Machine learning algorithms could be trained to recognize specific fragmentation patterns associated with particular structural motifs, thus facilitating the rapid identification and characterization of unknown compounds. Additionally, AI-driven approaches could also help predict reaction outcomes and optimize reaction conditions, leading to more efficient and selective lignin conversion processes.

Further challenges and opportunities also exist in the computational exploration of liquid−solid lignin depolymerization catalysis processes. Currently, theoretical and modeling studies in this field are still in their infancies, primarily due to the complexities introduced by solvent effects. Solvents significantly influence liquid−solid heterogeneous catalysis in several ways: they interact with the reaction transition state, lower its free energy, affect mass transfer, diffusivity, and solubility, and may compete with reactants for adsorption sites on the catalyst or act as active species themselves, altering the chemical nature of the surface. Moreover, liquid−solid reaction systems involve both complex heterogeneous catalysts and condensed phases, rendering the harmonic approximation for estimating partition functions and free energies inadequate. This situation highlights the need for new, computationally feasible quantum chemistry methods to accurately assess solvation effects on reaction and activation energies at liquid−solid interfaces. To effectively simulate these catalysis reactions, it is essential to consider kinetic and diffusion effects, as well as the dynamic changes in surface environments brought about by the liquid solvent.

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Notes

The authors declare no competing financial interest.

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