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Perspective

Protection Strategies for the Conversion of Biobased Furanics to Chemical Building Blocks

Ferdy J. A. G. Coumans, Zhanna Overchenko, Jan J. Wiesfeld, Nikolay Kosinov, Kiyotaka Nakajima,* and Emiel J. M. Hensen*

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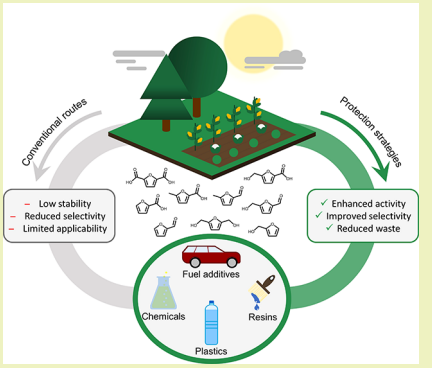
ABSTRACT: In recent years, the urgency to replace fossil-based resources by renewable biomass for obtaining chemical building blocks has only increased. Carbohydrate-derived furanic compounds are regarded as promising platforms for a renewable value chain. The high reactivity of such biobased intermediates requires the development of novel catalytic chemistry to enhance product yield. The protection of reactive functional groups provides a way to improve the product selectivity. Such protection strategies are common practice in the synthesis of fine chemicals and pharmaceuticals but are not fully explored for the conversion of furanic compounds. In this perspective, several examples of protection strategies focusing on the selective passivation of 5-HMF are discussed. Formation and removal of these protection groups are highlighted as well as the application of the neutralized 5-HMF in further processing. A guide for selecting the appropriate protection strategy depending on the targeted chemistry and operating conditions is provided.



KEYWORDS: *Biomass, Chemical building blocks, Furanics, Humins, Side reactions, Protection*

INTRODUCTION

The global temperature rise due to anthropogenic greenhouse gas emissions is expected to increase further in the coming century.[1] The recent IPCC report provides compelling evidence for the strong correlation between CO_2 emissions and global warming.[1] A viable contribution to achieve net zero CO_2 emissions is to substitute fossil resources by renewable biomass. To realize this, efficient technologies need to be developed to convert (preferably) nonfood sources and related waste streams into value-added chemicals and fuels.[2] Similar to the oil refining and petrochemical industry, such processes will be centered around a limited number of platform molecules that can be easily obtained from abundant biomass sources and converted to a wide range of fuels, chemicals, and materials. For example, furanics can be readily extracted from carbohydrates, among which furfural and 5-hydroxymethylfurfural (5-HMF) are prominent examples.[2−4] Specifically, 5-HMF is a versatile chemical that can be used as a green intermediate for current industrially relevant processes (drop-in) as well as novel, fully biobased routes.[4−7] Typically, lignocellulosic biomass is first separated into cellulose, hemicellulose, and lignin (Figure 1). The holocellulosic fraction is converted further into hexoses and pentoses, after removing the lignin part. Subsequent dehydration of these carbohydrates yields various furanic compounds, which can be further upgraded into chemical building blocks.[8,9]

In comparison to fossil-based feedstocks, furanic compounds are more reactive due to the presence of functional groups.[5] Hence, alternative chemical conversion routes, including catalysts and reactor concepts, need to be developed. The intrinsic reactive nature of furanics requires the use of milder temperatures and, henceforth, mostly liquid-phase operation to avoid unwanted production of side products like insoluble humins.[5,10] Petroleum-based processes, on the other hand, often employ elevated temperatures and gas-phase operation to activate C−H bonds. Although significant efforts have been made to develop catalytic systems and optimize process conditions, practical implementation of furanics as a feedstock on a large-scale remains limited.[11,12] Humin formation can be mitigated to some extent by operating in dilute solution or by working in biphasic systems, in which the valuable product is extracted in an organic phase. The instability of furanic compounds is not only problematic for practical implementation of conversion processes, even long-term storage can lead to formation insoluble humins.[13−15] In contrast, fossil feedstocks can be stockpiled, with little change in chemical composition,

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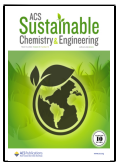

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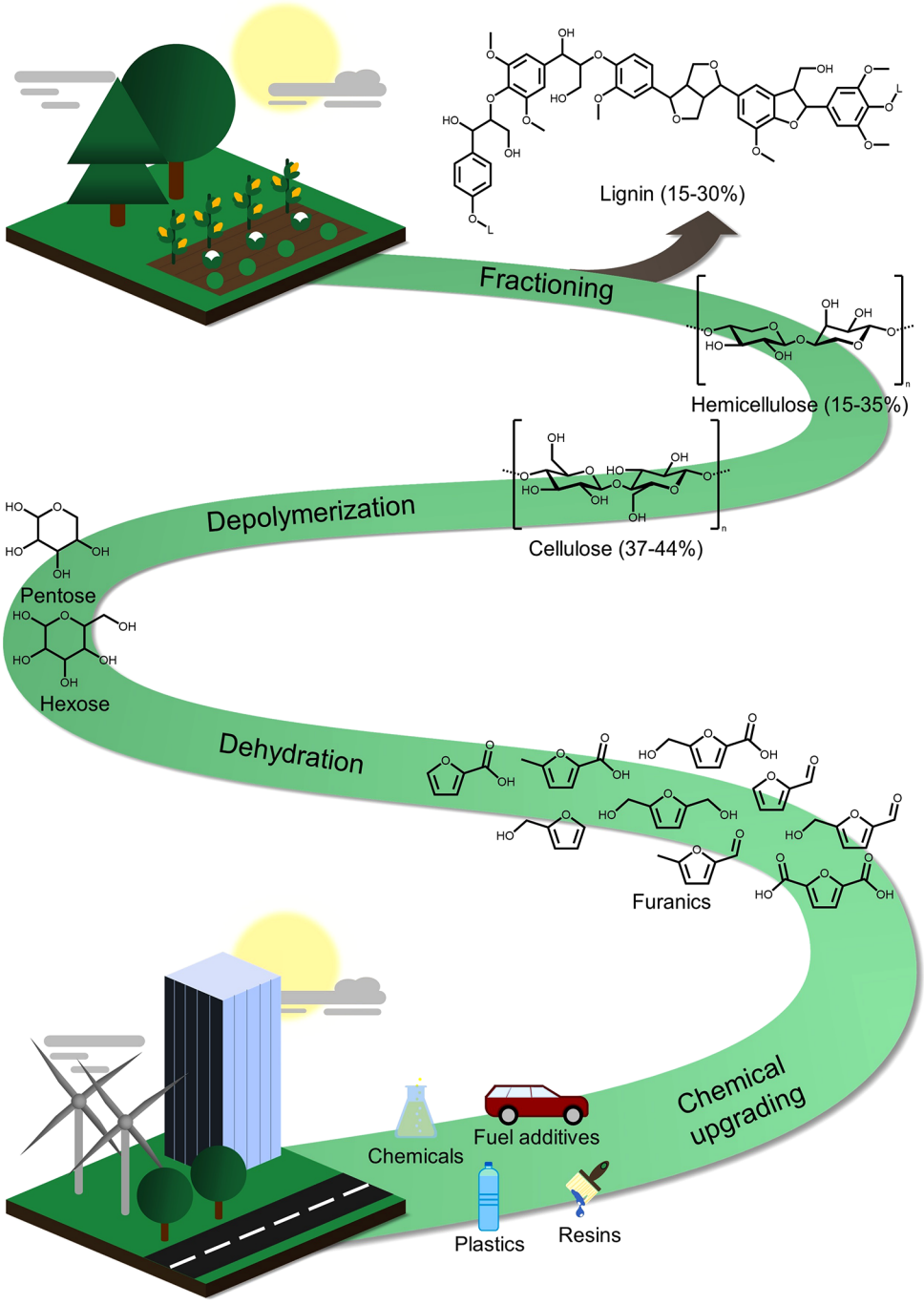

Figure 1. Production of sustainable chemicals and fuels from furans. The presence of additional functionalities makes these oxygenates suitable platform molecules for the chemical industry.

almost indefinitely for later use. A viable approach to avoid the undesired decomposition of, for example, 5-HMF is to convert it toward more stable molecules such as 2,5-dihydroxymethylfuran, 2,5-dimethylfuran, 5-methylfurfural, or furfuryl alcohol.[16−18] The partial or complete removal of the oxygen functionalities makes these compounds directly suitable for fuel additives. From a chemical perspective, however, efficient conversion of platform molecules, such as 5-HMF, to valuable base chemicals is more interesting, especially when a large part of the functional groups can be retained in the final product.[19] In view of this, protection/deprotection strategies can temporarily passivate reactive groups without their complete removal.[20] Such chemical modifications to obtain chemoselectivity in subsequent reactions are widely used in multistep organic syntheses. Approximately 21% of all synthesis steps in the manufacture of medicine involves a protecting group.[21,22] Also in the conversion of sucrose into the sucralose, part of the primary alcohol groups is acetylated prior to final chlorination.[23]

Applying protection strategies to valorization of 5-HMF and other furanics imposes a set of criteria for the selection of the optimal strategy. Foremost, the protection and deprotection should adhere to the principles of green chemistry.[24,25] As biobased feedstocks aims to replace traditional fossil-derived molecules, the protection method should be selective and

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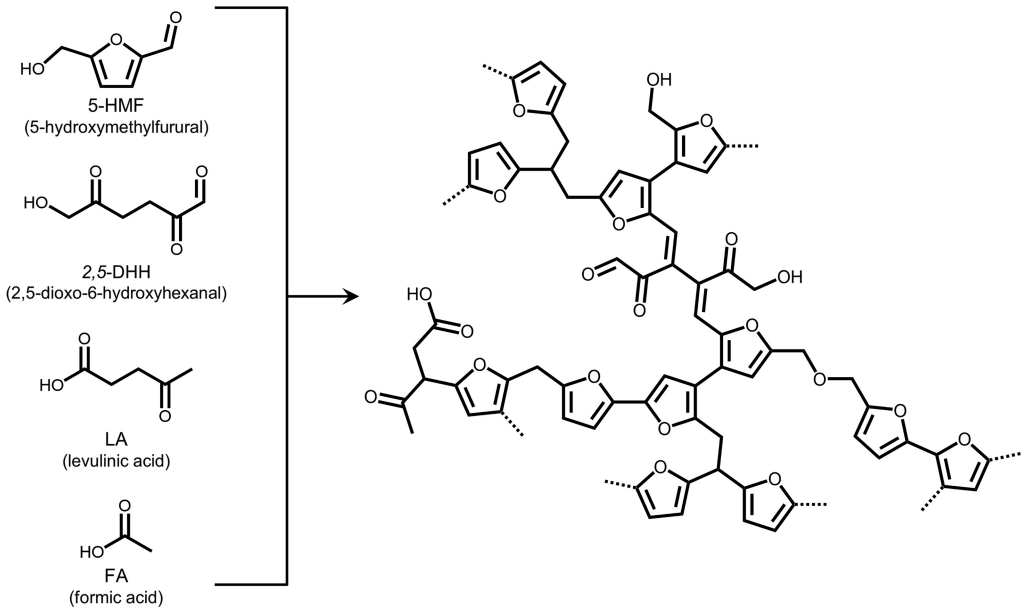

Figure 2. Proposed structure of glycose-derived humin. Main constituents are 5-HMF (5-hydroxymethylfurfral) and 2,5-dioxo-6-hydroxyhexanal (2,5-DHH) while only limited amounts of acids, like levulinic acid (LA) and formic acid (FA), are incorporated. Humin structure has been adapted from the literature.[35]

involve readily available and nontoxic reagents. It is furthermore essential that the selected strategy uses chemicals that can be readily recycled and are preferably biobased. In general, employing protection strategies decreases the atom efficiency of the process, which in principle increases the process costs and environmental burden.[26] These drawbacks need to be offset by improvements in process intensification and reaction kinetics, rendering the modified approach beneficial over the conventional process. Atom economy is defined as the ratio between the molecular weight of the product and the sum of the molecular weights of all reactants.[24] For example, the atom economy of the synthesis of BILN2061, which is an active pharmaceutical ingredient, decreased from 96% to 84% when a *t*-butoxycarbonyl (*t*-BOC) protecting group was employed.[27,28] However, the reaction of the protected intermediate could be operated at a 20 times higher substrate concentration and a much lower catalyst loading, making the new synthesis approach economically feasible. Even though these strategies offer great value in terms of substrate stabilization, research into the conversion of protected furanics is still relatively novel. This may be in part due to the need for expertise in synthetic organic chemistry, catalysis, and process engineering to render a viable approach. Nevertheless, protection strategies have the potential to reduce waste production by increasing product selectivity. To illustrate this, relevant examples for protection of 5-HMF are discussed. This platform molecule is the most studied and contains relevant functional groups that are present in other furanic compounds as well (Figure 1). We first underline the complexity of biomass valorization by focusing on the humin formation. Common protection strategies (namely, acetalization, etherification, and esterification) as well as some other methods are discussed with a focus on the protection/deprotection steps and possible applications. Finally, this perspective provides a guide to select suitable protection strategies when targeting different chemistries.

HUMIN FORMATION

The higher oxygen content of biobased feedstocks, in comparison to the hydrocarbons obtained from crude oil, is especially interesting for the production of chemical building blocks. However, the presence of reactive oxygen-containing groups renders biobased molecules prone to unselective side reactions, leading to less interesting high-molecular weight products. For example, activation energies for the dehydration of glucose and fructose to 5-HMF are in the similar range as those for oligomerization toward humins.[8] Even in the processing of 5-HMF toward compounds like levulinic acid, activation energies were observed to be comparable as those for humin formation.[8] IR studies highlighted the similarity between humins obtained from glucose and fructose.[29,30] It was estimated that around 60% of the humins is made up from furanic rings.[31] The mechanism of humins formation is very complex. It has for instance been postulated that carbohydrates are converted first to 5-HMF and subsequently hydrolyzed to 2,5-dioxo-6-hydroxyhexanal (2,5-DHH).[32] This reactive intermediate would then polymerize further to humins via aldol addition/condensation reactions.[30] In fact, the amount of solid product was found to be dependent on the ease of 5-HMF formation (D-fructose > D-glucose) as well as acid concentration and reaction temperature.[33,34] On the basis of ^{13}C-labeled NMR measurements, a refined humin model has been proposed (Figure 2).[35] The conversion of 5-HMF gives rise to a larger amount of humins than, for example, furfural and furfuryl alcohol.[36] This higher extent of oligomerization is likely due to the presence of hydroxyl and carbonyl functionalities. Initial dimers of 5-HMF are formed via self-etherification or etherification with formic acid (FA) and levulinic acid (LA).[14,15] The free carbonyl group remains available for aldol and acetalization reactions, leading to the formation of larger fragments and finally humins. The high susceptibility toward side reactions limits the valorization of 5-HMF to valuable chemical building blocks on a larger scale. Most studies therefore still rely on diluted furan solutions or use mild reaction conditions. However, this severely impedes

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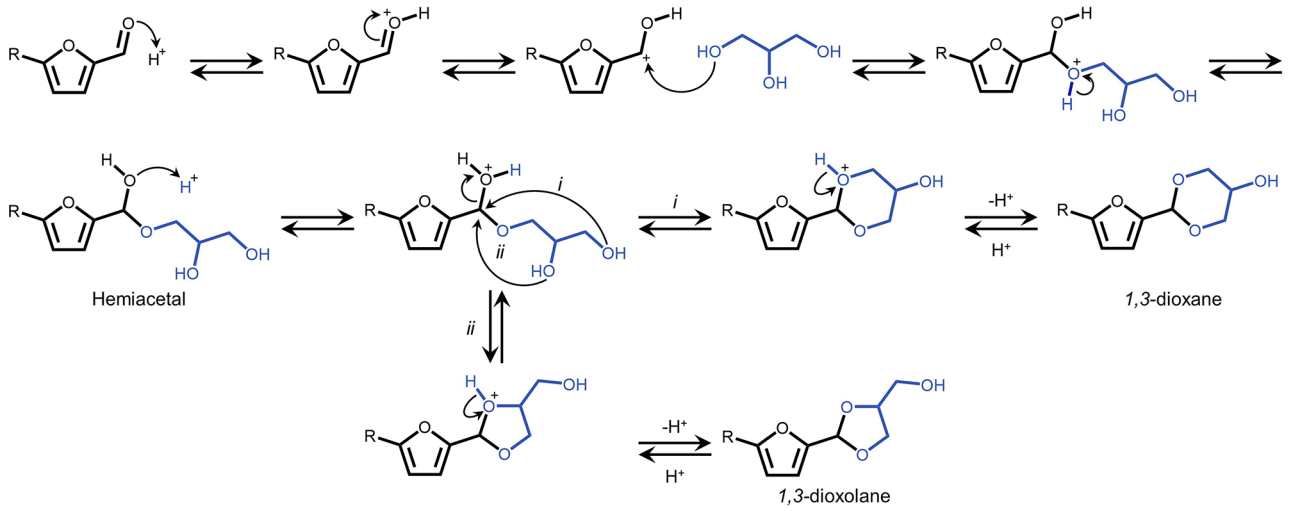

Figure 3. Acid-catalyzed acetalization of substituted furfuraldehyde with a glycerol. The triol can react via the 1,3-addition (i) as well as the 1,2-addition (ii). Since all reaction steps are in equilibrium, the 1,3-dioxane can be interconverted into the 1,3-dioxolane and vice versa.[44]

practical implementation that relies, in general, on short reaction times and operation at high concentrations to limit solvent recycle. Therefore, temporarily passivating the highly reactive groups in furanic compounds using chemical protection strategies might be a suitable method to obtain the desired product selectivity under more industrial relevant conditions.

PROTECTION STRATEGIES

The availability of suitable protection strategies depends on the type of functionality, which for furanic compounds is limited to mostly carbonyls, hydroxyls, and carboxyls (Figure 1). In this section protection strategies targeting 5-HMF are discussed, as this platform molecule contains most of the relevant functional groups. For example, the carbonyl functionality is often protected using acetals, while the hydroxyl group is mainly etherified. In case 5-HMF underwent an oxidative treatment in advance, esters are a viable option to modulate the reactivity. Furthermore, some uncommon methods are highlighted at the end of the section.

Acetalization. Acetals are functional groups in which the central carbon atom is connected to two alkoxides and two organic fragments of which one might be a hydrogen. Acetalization is mainly used to protect carbonyl functionalities by reaction with alcohols to acetals or ketals.[37−43] The central acetal carbon has a tetrahedral orientation, without changing the initial oxidation state, thereby enhancing the stability of the resulting product. Different types of alcohols can be used for the acetalization, opening up the possibility to tune the properties of the acetal. Symmetric acetals, for example, are obtained when acetalizing with a single type of alcohol, while a combination of alcohols yields mixed acetals where the central carbon atom can be linked to different alkoxides. The use of diols or triols results in the formation of cyclic acetals, which are often found to be more stable than their acyclic counterparts.

Protection. As can be seen in Figure 3, each step of the acetalization reaction is reversible. Therefore, often *in situ*-formed water is removed or an excess of the alcohol is used to drive the reaction to completion. The stability of the reagents and products dictates the reaction conditions, although often organic solvents (e.g., dichloromethane or benzene) and elevated temperatures are employed. For example, the acetalization of furfural with glycerol can be carried out under reflux conditions in benzene,[41] whereas the same reaction with 5-HMF needs to proceed at room temperature to mitigate humin formation.[37] The frequent application of harmful solvents might form a major hurdle for industrial applications. More green and sustainable alternatives must be implemented to make the transition to industrial scale for this type of protection strategies.

In order to initiate the acetalization, the carbonyl group is often activated by either a Brønsted acid (e.g., Amberlyst-15 or *p*-sulfonic acid) or a Lewis acid (e.g., metal triflates).[37,41] Figure 3 shows that the initiation is followed by nucleophilic addition of the desired alcohol leading to the formation of a hemiacetal. Upon the removal of water, the resulting carbocation can form the acetal when subsequently reacting with a second OH group. The stability of acetalized furanic compounds depends on the chosen acetalization agent (i.e., alcohol). In general, acyclic acetals from mono-ols (e.g., methanol) are less stable compared to the cyclic acetals. Hydrolysis of the acyclic acetals are entropically favored.[44] It was observed that the acyclic 5-HMF acetals derived from methanol readily decomposed (∼96%) after 2 h at 473 K under vacuum.[37] The stability can be improved by forming cyclic acetals, still around 72% of the 5-HMF protected by 1,2-ethanediol degraded under similar reaction conditions. In contrast, a six-membered ring cyclic acetal derived from 1,3-propanediol was more stable, and only 25% of the protected compound decomposed after 2 h at 473 K under vacuum.[37] Combined experimental and theoretical work showed that the six-membered ring acetal of 5-HMF is thermodynamically favored over the 1,2-ethaniodiol-derived acetal.[37] When using glycerol as the acetalization agent, both the 1,2-dioxolane (1,2-addition) and the 1,3-dioxane (1,3-addition) acetal can be obtained (Figure 3) due to the presence of an additional secondary OH group.[40,42,43] The selective formation of either moiety depends on the chosen reaction conditions. In general, higher reaction temperatures favor the formation of 1,3-dioxane.[41] Nonetheless, the five-membered acetal is usually formed (52%−78%) as the kinetically favored product, while the six-membered ring is thermodynamically favored.[40−43] Formation and stability of acetals are strongly influenced by steric and electronic effects.[45,46] For example, the 1,3-dioxane obtained by using 1,3-propanediol is favored for benzaldehyde,

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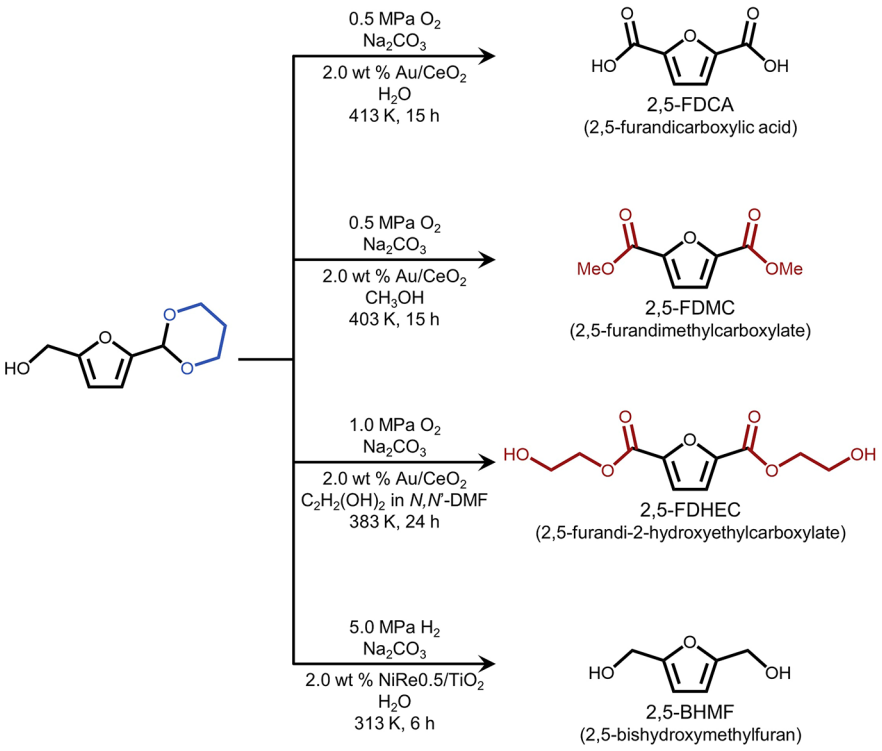

Figure 4. Acetalized 5-HMF can be used in both oxidation and reduction reactions to obtain 2,5-FDCA (and derivatives) and 2,5-BHMF.

whereas the 1,3-dioxolane is preferentially formed with acetophenone and 1,2-ethanediol.[47]

Application. The most prominent use of acetalized furanic compounds thus far is in the production of 2,5-furandicarboxylic acid (2,5-FDCA) or its derivatives. Figure 4 depicts some pathways to these biobased monomers from the six-membered ring acetal of 1,3-propanediol and 5-HMF. The oxidation was carried out in concentrated substrate solutions (~10−20 wt %) at 473 K in the presence of Au/CeO_2 catalyst and Na_2CO_3.[37] The addition of a proton scavenger (i.e., an elevated pH), such as Na_2CO_3, is important to neutralize any formed H^+ that otherwise might promote side reactions. DFT calculations showed that the mild Lewis acidity of the ceria support is sufficient to slowly liberate the aldehyde functionality, thereby facilitating the oxidative dehydrogenation. Under these conditions, yields of 90%−95% 2,5-FDCA were obtained. Kinetic studies revealed that oxidation of acetalized 5-HMF starts with the conversion of its hydroxy group to the carboxylic acid. The reaction rate for the conversion of the aldehyde intermediate was found to be significantly larger than the initial oxidation of the hydroxy group.[37] This results in less byproduct formation as compared with the oxidation of unprotected 5-HMF. The overall reaction rate was found to be dependent on the final oxidation step of the acetal moiety. The acetal is partially hydrolyzed by hydroxide to the hemiacetal, which is catalyzed by Lewis acid sites of the ceria support.[37] DFT calculations demonstrated that it is energetically more favorable to form the 2,5-FDCA monoester, via oxidative dehydrogenation using molecularly adsorbed O_2, than the free 2,5-FDCA product. With unprotected 5-HMF at higher concentrations, formation of humins and oxidation to nondesired products were dominant.[37] DFT calculations showed that the rate of oligomerization of 5-HMF leading to humin formation was higher than the initial oxidation step to the 5-HMFCA intermediate.

The high propensity of 2,5-FDCA to undergo side reactions during polymerization with 1,2-ethanediol into polyethylene furanoate (PEF) favors the use of less reactive monomers. For example, acetalized 5-HMF was used in the Au/CeO_2-catalyzed oxidative esterification with methanol or 1,2-ethanediol (Figure 4).[38] The resulting 2,5-furandimethylcarboxylate (2,5-FDMC) ester could be obtained in yields greater than 90% using 16.7 wt % (acetalized 5-HMF in methanol) solutions after 15 h. A catalytic amount of water added to the reaction mixture is key in efficiently converting the six-membered ring acetal, as this step is rate determining. Formation of 2,5-furandi-2-hydroxyethylcarboxylate (2,5-FDHEC) from 1,2-ethanediol was limited (45% yield), even when using passivated 5-HMF. Application of an inert cosolvent, like *N,N′*-dimethylformamide (*N,N′*-DMF), significantly improved the 2,5-FDHEC yield to 80%−90%. Again, the beneficial role of the acetal protection group was demonstrated by a significantly improved performance. The difference between the transformations of protected and unprotected 5-HMF was especially noticeable at higher concentration (~10 wt %). 5-HMF yielded 4% 2,5-FDMC and 5% 2,5-FDHEC, whereas yields of 92% and 91% were achieved with acetalized 5-HMF, respectively.[38] Similar to the oxidation reaction, the use of an acetal protection group influenced the reaction kinetics. Reaction rates for the initial oxidation step were larger for protected 5-HMF than for the free 5-HMF, while side reactions occurred at higher rates for the later reactant.[38] DFT calculations highlighted that the acetal will only be partially hydrolyzed on Au/CeO_2. Full conversion toward 2,5-FDMC is achieved by transesterification with the solvent. Adding small amounts of water to the reaction mixture accelerated the final step. These results indicate the delicate interplay between oxidation and hydrolysis reactions, which can be tuned by controlling the pH.

In recent years, electrochemical methods for the production of 2,5-FDCA and derivatives have also been investigated.[48,49]

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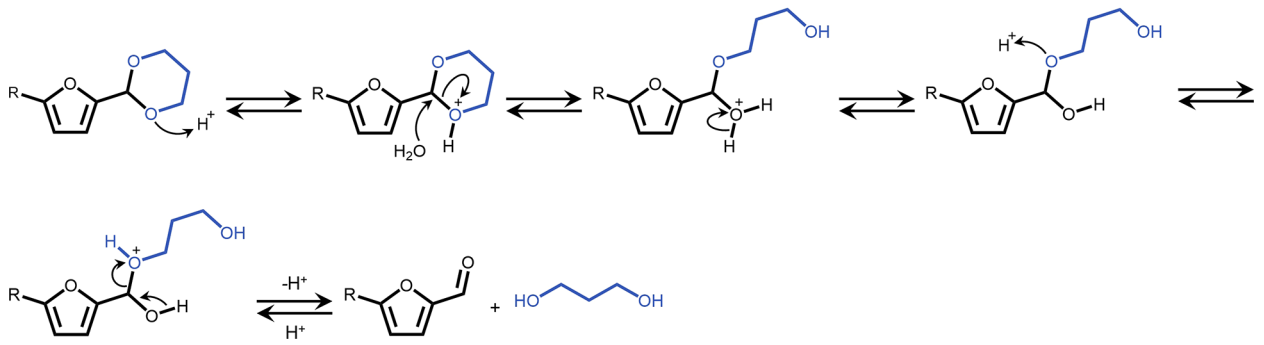

Figure 5. Acid-catalyzed hydrolysis of the acetal results in the liberation of both the furfuraldehyde moiety and the hydroxyl compound.[46]

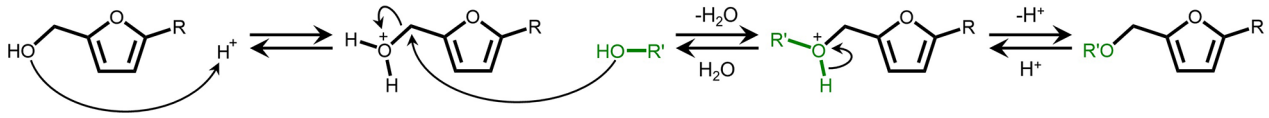

Figure 6. Acid-catalyzed etherification of furfuryl alcohol with a hydroxyl group-containing molecule. Often the solvent (i.e., alcohol) is used as the etherification agent.[55]

Electrocatalytic oxidation can offer a cleaner (i.e., lower byproduct formation) and safer process. However, often large quantities of base are needed, and as in conventional approaches, dilute feeds are used to suppress unwanted side reactions. For 5-HMF, electrochemical oxidation mainly yields the partially oxidized 5-formylfurancarboxylic acid (5-FFCA), while 2,5-FDCA can only be obtained for relatively long residence times.[48] Another drawback is that 5-FFCA remains in the product stream, which would require tedious and expensive crystallization steps to remove the monoacid.[50] Thus far, acetals have not been investigated as protection groups in the electrochemical oxidation toward 2,5-FCDA. Besides this, such a strategy may also find utility as a purification step after thermocatalytic oxidation (see the Etherification section).[50]

In the examples discussed above, the acetal group is removed during the oxidative treatment. In contrast, the protective group remained stable under reducing atmospheres. Therefore, an intermediate deacetalization step is necessary prior to the hydrogenation reaction. For example, both 2,5-bishydroxymethylfuran (2,5-BHMF) and 2,5-bishydroxymethyltetrahydrofuran (2,5-BHMTHF) were readily obtained, once carbonyl group was liberated (Figure 4).[39] These compounds are potential monomers for biobased plastics such as polyesters and as a precursor for 1,6-hexanediol in the case of 2,5-BHMTHF, specifically. Careful control of the deprotection rate proved to be vital in obtaining high yields. A too fast deprotection rate resulted in a high 5-HMF concentration, leading to humin formation, whereas a slow rate resulted in ring hydrogenation. The deprotection rate was controlled by tuning the appropriate pH of the reaction solution (e.g., by adding appropriate amounts of base like Na_2CO_3).[39] The benefits of the acetalization strategy and controlled deprotection was again highlighted by a notably improved performance using the acetalized 5-HMF. The yield of 2,5-BHMF increased from 18% to 79%, whereas the 2,5-BHMTHF yield became 50 times higher (from 0.1% to 5%).[39] Noteworthy, high levels of 1,3-propanediol (between 76% and 94%) could initially be recovered. After optimization of the reaction conditions and catalysts, more than 90% of the acetalization agent was regained at conversion levels above 98%. The ease of recycling the diol would make this reaction interesting for large-scale application, in which the reagent can be fed back in the process stream.

Deprotection. In general, acetalized furanic compounds are stable against various nucleophiles and under alkaline conditions.[51] Since acetalization is a reversible reaction, deprotection can be carried out in a similar fashion as their initial formation. Liberation of the carbonyl group can proceed via hydrolysis in the presence of Brønsted or Lewis acids (Figure 5). A high degree of deprotection can be achieved through the use of an excess H_2O or removal of the liberated alcohol. Control over the deprotection rate can be exerted by optimizing the reaction conditions like adjusting the pH or tuning the acid strength of the catalyst. As was shown by synthesis of 2,5-FDCA and 2,5-BHMF, furanic acetals can be converted under oxidative and reductive conditions. Recovery of the acetalization agent is key to make this approach of practical importance. It was shown that approximately 20% of the diol is lost during oxidation with minor amounts of 3-hydroxypropionic acid and 3,3′-oxidipropionic acid being formed.[37] In contrast, more than 90% of the diol can be recovered after the hydrogenation reaction to 2,5-BHMF.[39] To improve the recovery of the acetalization agent, a stepwise oxidation approach or continuous extraction of the alcohol from the reaction mixture could be considered.

Etherification. Ethers are chemical bonds that consist of two hydrocarbon moieties connected through an oxygen atom. These types of linkages can either be symmetric, obtained through self-etherification of the substrate, or asymmetric when another hydroxyl compound is present during the reaction. Generally, the ether bond is very stable under acidic conditions (except in strong acids such as hydroiodic acid) and do not react with alkali metals.[52] In the literature, etherified furanic compounds, like 5-ethoxymethylfurfural (5-EMF), have been mainly aimed to be used as fuel additives by raising the boiling point and octane number.[53,54] As a result, the ether is maintained in the final product, and therefore, de-etherification is usually not pursued.

Protection. The most common synthetic method to obtain ethers is via the Williamson procedure, in which the alcohol is deprotonated first by a strong base (e.g., metal hydrides) and subsequently reacts with an alkyl halide.[55] Thus far, the Williamson method has not been reported extensively for

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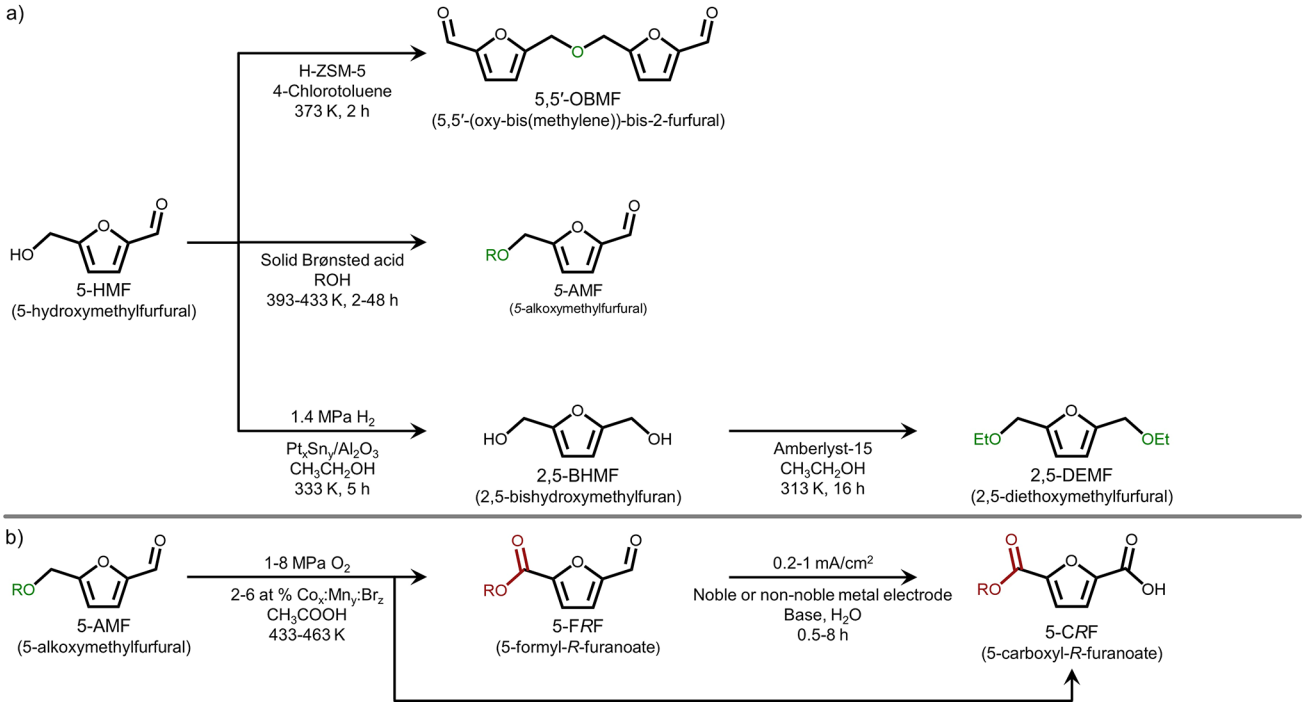

Figure 7. (a) Ethers of 5-HMF can form either via self-etherifcation or via etherification with a secondary hydroxyl compound. Dietherification requires an intermediary hydrogenation step to convert the carbonyl group priorly. (b) Oxidation of 5-HMF ether to 2,5-FDCA derivatives. A second electrochemical oxidation step is employed to convert any residual partially oxidized compounds to the final product.

furanic compounds. To the best of our knowledge, only the etherifications of 5-HMF and 5-ClMF (5-chloromethylfurfural) in the presence of potassium iodide and potassium carbonate have been reported.[56,57] A 43% yield of the 5,5′-(oxy-bis(methylene))-bis-2-furfural (5,5′-OBMF) could be obtained. However, equimolar amounts of salts were used to carry out the reaction.

The more common etherification method for 5-HMF relies on activation of the hydroxyl group by a proton (usually a solid acid like a zeolite). Protonation of the OH group is followed by the nucleophilic addition of a second alcohol and the removal of water (Figure 6).[52] Furthermore, etherification is often carried out in which the solvent also acts as the reagent as well. This ensures that the reaction will achieve almost full conversion toward the etherified furanic compound. Although each of the steps is in theory reversible, breaking of the final ether bond requires strong acidic conditions.

Application. The choice of etherification agent is usually determined by the targeted product specifications. For example, the self-etherification of 5-HMF in the presence of a solid Brønsted acid, like H-ZSM-5, yields 5,5′-OBMF (Figure 7a).[58] This compound is useful as a precursor for imine-based polymers as well as an antiviral agent against hepatitis. Yields up to 90% have been reported, and the conversion correlates with the concentration of Brønsted acid sites. In contrast to the Williamson procedure,[56,57] waste salt formation is limited, and the solid catalyst can be simply collected and regenerated for reuse. However, in this study, 4-chlorotoluene was used as a solvent, which limits its application in any green process.

Etherifications can also be performed in the presence of an additional alcohol, like ethanol or *t*-butanol, to form the corresponding 5-alkoxymethylfurfural (5-AMF).[53,59−61] In general, the reaction rate strongly depends on the size: ethanol > 1-butanol > cyclohexanol.[51] Similar to self-etherification, most etherification reactions are catalyzed by solid Brønsted acids. Yields between 52% and 72% have been reported for 5-ethoxymethyl-furfural and 5-*t*-butoxymethyl-furfural (Figure 7a).[59,60] Interestingly, the use of a solid catalyst in combination with a solvent, acting as the etherification agent, would allow continuous operation. However, this has not been investigated yet.

When etherification of both the hydroxy and carbonyl functionality in 5-HMF is targeted, an intermediate hydrogenation step is required.[61] As shown in Figure 7a, 2,5-bishydroxymethylfuran (2,5-BHMF) was obtained first using a Pt_xSn_y/Al_2O_3 catalyst, followed by etherification of the furanic diol with ethanol toward 2,5-diethoxymethylfurfural (2,5-DEMF) in the presence of a protonic Amberlyst-15 resin. Although the two stages can be combined into a single reductive etherification step, the yield of the final diether was significantly lower (sequential 85% vs simultaneous 59%). It was found that the presence of an acidic catalyst during the hydrogenation reaction leads to side reactions, which lowered the selectivity toward the desired diether.[61]

Instead of etherifying 5-HMF, different 5-AMF compounds can be obtained when glucose is dehydrated in the presence of an alcohol and acid catalyst.[62] This is a major advantage as the synthesis is carried out in one single step, and 5-HMF becomes partially passivated. In the past decade, several patents reported the oxidation of 5-HMF ethers toward 2,5-FDCA and esters (Figure 7b).[63,64] The reaction relies on the use of Co/Mn/Br salts as catalysts, O_2 as oxidant, and a carboxylic acid (e.g., acetic acid) solvent. High selectivity of the oxidized products (between 70% and 85% at full conversion) are reported with feed concentrations up to 11 wt %.[63,64] Oxidation of ethers derived from methanol resulted in higher amounts of the monoester, whereas 5-EMF yields mainly 2,5-FDCA.[64] Although high 2,5-FDCA yields were reported, significant amounts of intermediate

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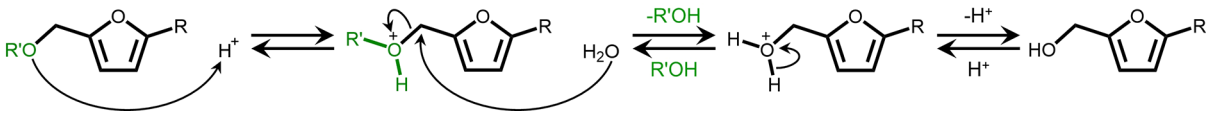

Figure 8. Deprotection of a furanic ether via acid-catalyzed hydrolysis.[55]

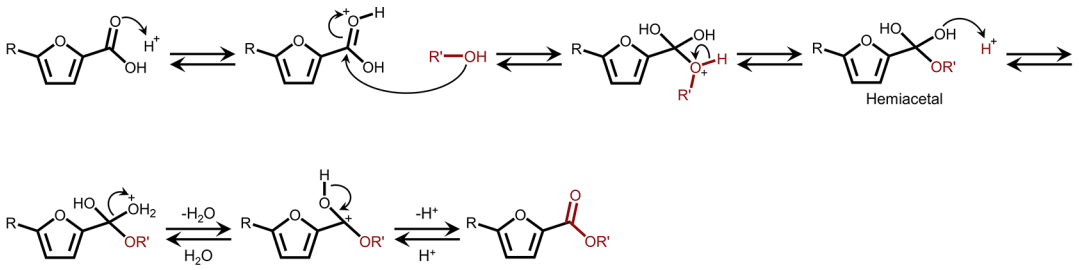

Figure 9. Acid-catalyzed esterification of a furancarboxylic acid and a secondary hydroxyl compound.[68,69]

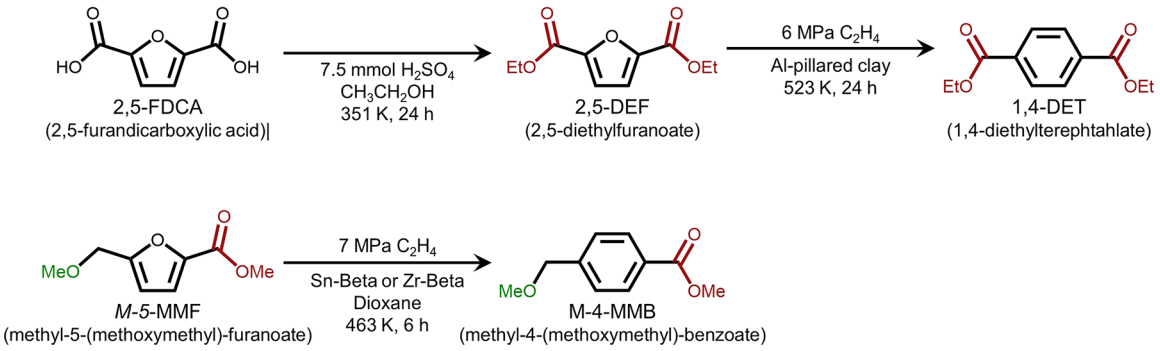

Figure 10. Formation of terephthalic acid and derivatives from furancarboxylic acids or esters via the Diels−Alder cycloaddition (DAC).

products like the 5-formyl-*R*-furanoate (5-F*R*F, with *R* being the alkyl chain) remained present. Removal of these partially oxidized compounds is cumbersome, making a secondary oxidation desirable.[48,50] To avoid a second (thermocatalytic) step requiring higher reaction temperatures and thus resulting in a lower selectivity, an electrochemical procedure has been developed.[50] This approach was found to be robust, as full conversion of the intermediate can be achieved in the presence of 5-HMF, 2,5-diformylfuran (2,5-DFF), or 5-hydroxymethyl-furancarboxylic acid (5-HMFCA). This would render yield maximization of the first oxidation step unnecessary. Streams with up to 10 wt % of partially oxidized 5-HMF compounds can be readily converted by adjusting the residence time. Suitable electrocatalysts comprise both noble (i.e., Pt, Ag) and non-noble (i.e., Fe, Ni) metals. The aqueous electrolyte should be alkaline as hydroxides are required for the oxidation and solubizes the products. Recovery of the electrolyte could be improved by using a trialkylamine base instead of a hydroxy salt. Although this process is an example of combining different areas of expertise, still some improvements with respect to the green chemistry principles can be made. For example, the use of heterogeneous catalysts or more environmentally benign oxidants in the primary oxidation step would be desirable.

Deprotection. As stated earlier, deprotection of etherified furanic compounds is generally not pursued. Nonetheless, ether bonds can be cleaved under certain conditions, even though they are very stable functional groups, for example, at high temperatures and in the presence of catalysts such as aluminum oxide.[52] Deprotection can also be carried out via hydrogenolysis involving noble metal catalysts.[51] Also strongly acidic conditions can hydrolyze the ether bond (Figure 8).[55] However, the harsh reaction environment will most likely lead to undesirable side reaction, and therefore, the ether functionality is typically retained in the final product.

Esterification. Esters are bonds derived from the reaction between a carboxylic acid and hydroxyl compound. Incorporation of such functional groups can improve the solubility in aqueous solutions and lower their boiling point, which eases both processing and product analysis. Although the hydroxyl group in 5-HMF can in theory be esterified, the high reactivity of 5-HMF under acidic conditions, leading to humin formation, limits its applicability as a hydroxy donor. Therefore, the compound is preferable oxidized first toward 5-hydroxymethyl-furancarboxylic acid (5-HMFCA) or 2,5-furandicarboxylic acid (2,5-FDCA) and subsequently reacted with an alcohol.[65−67] Similar to the ethers, ester functionalities are often retained in the final product due to the aforementioned benefits.

Protection. As can be seen in Figure 9, esterification starts with the protonation of the furancarboxylic acid moiety.[68] Although the reaction can be carried out under basic conditions, the widespread availability of solid Brønsted acids makes the acid-catalyzed approach the preferred route for furanic compounds. Following the initial activation, nucleophilic addition of the hydroxyl compound yields a hemiacetal intermediate.[69] With the release of water, the final furanoate ester is obtained. Similar to the previous examples, all esterification steps are reversible, and therefore, an excess of reagents or removal of liberated water can direct the reaction to completion.

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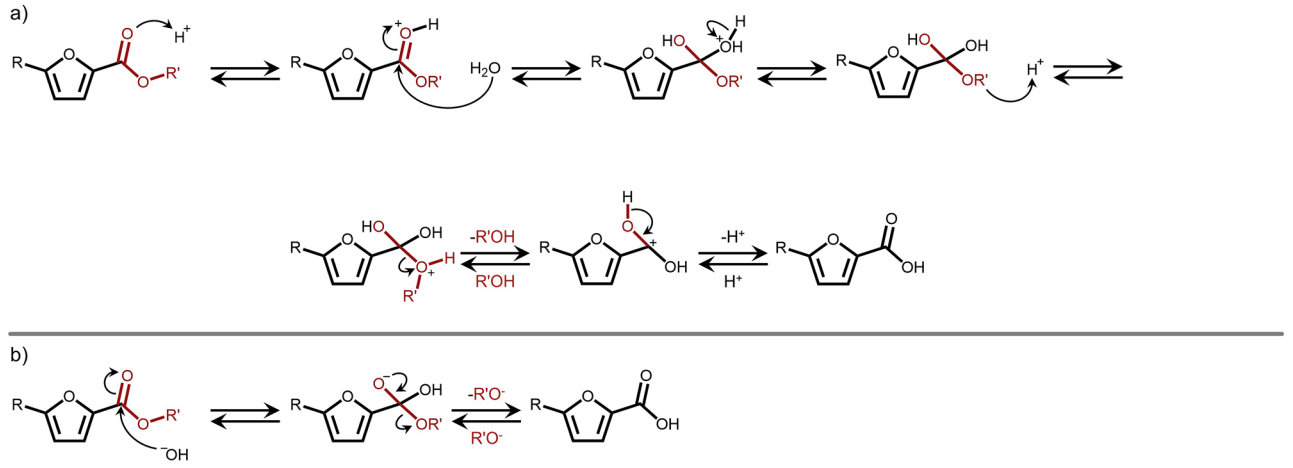

Figure 11. Ester functionality can be removed via (a) acid-catalyzed or (b) base-catalyzed hydrolysis.[69,72]

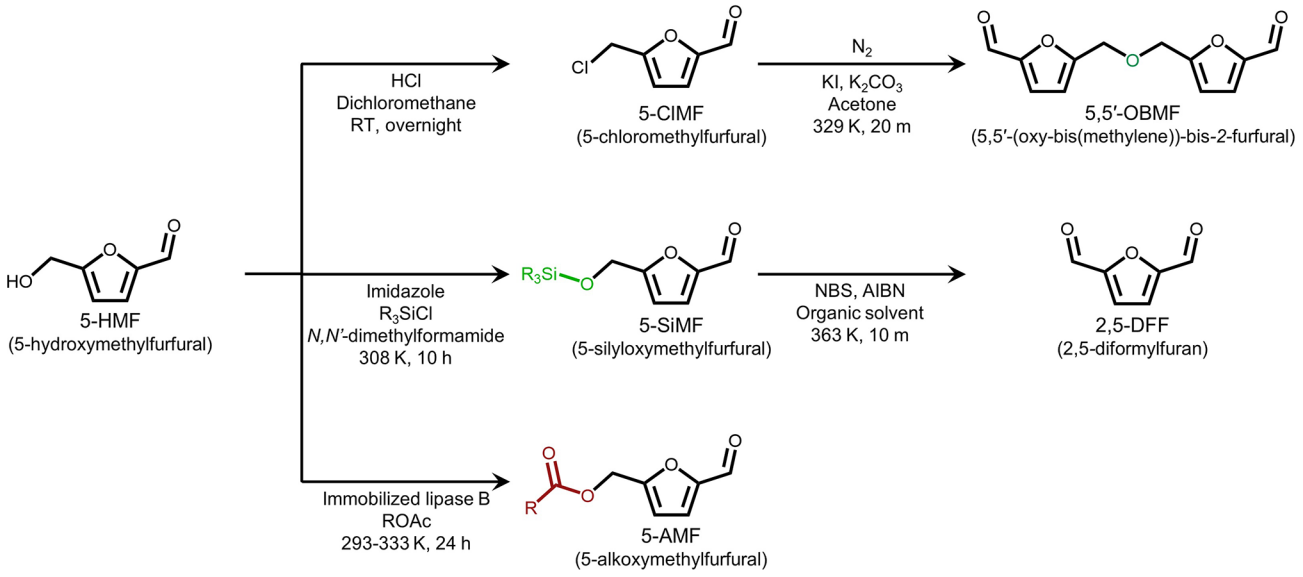

Figure 12. Alternative protection strategies for the passivation of 5-HMF.

Application. Thus far, esterification of 5-HMF focused mainly on the synthesis of 1,4-terephthalic acid (1,4-TPA) and derivatives (Figure 10). For example, 1,4-diethylterephthalate (1,4-DET) can be synthesized in a two-step procedure.[65] First, 2,5-diethylfuranoate (2,5-DEF) was prepared via the H_2SO_4-catalyzed esterification of 2,5-FDCA with ethanol, followed by the solid-state Diels–Alder cycloaddition (DAC) of 2,5-DEF and ethylene in the presence of Al-containing solid catalysts.[65] In this work, 2,5-DEF was preabsorbed to the catalyst, and the solvent was evaporated prior to the DAC reaction. Conversions of 66% with terephthalate selectivities toward 88% could be achieved. However, the solid-state approach would limit most practical applications due to the required solvent evaporation and product extraction.

In general, activity of the DAC reaction relies on the HOMO and LUMO of the diene and dienophile.[70,71] The strong electron-withdrawing character of both carboxyl groups in 2,5-FDCA impairs the DAC step, in which the furanic compound acts as the diene.[66] Therefore, the partially oxidized 5-hydroxymethylfurancarboxylic acid (5-HMFCA) was converted into 4-hydroxymethylbenzoic acid (4-HMBA) via the DAC with ethylene in the presence of a tin- or zirconium-containing beta zeolite (Sn-Beta or Zr-Beta).[66,67] The diene conversion increased from 16% to 61% with a 4-HMBA selectivity of 31%. Similar to previously discussed examples, the presence of multiple reactive groups can lead to side reactions. Therefore, the methanol-protected methyl-5-(methoxymethyl)-furanoate (M-5-MMF) has been investigated as a substrate as well. The selectivity toward methyl-4-(methoxymethyl)-benzoate (M-4-MMB) increased to 48% when using M-5-MMMF. Replacing Sn-Beta with Zr-Beta resulted in a M-4-MMB selectivity of 81% after 6 h of reaction, although the conversion decreased from 50% to 26%. In order to obtain the final terephthalate product, a final oxidation of the benzoate intermediate would be required. However, this step was not pursued in the reported studies.[66,67]

Deprotection. The deprotection of furanoate compounds has not been investigated yet. However, esterifications are reversible, identical to the previous strategies, and therefore, the carboxylic group can be regenerated via acid or basic hydrolysis.[72] A common deprotection approach is to heat the ester in excess of water in the presence of an acidic catalyst (Figure 11a).[73] The rate of hydrolysis depends on both steric and electronic factors, which is useful in the case of polyfunctionalized substrates.[51] In turn, base-catalyzed deprotection (Figure 11b) starts with

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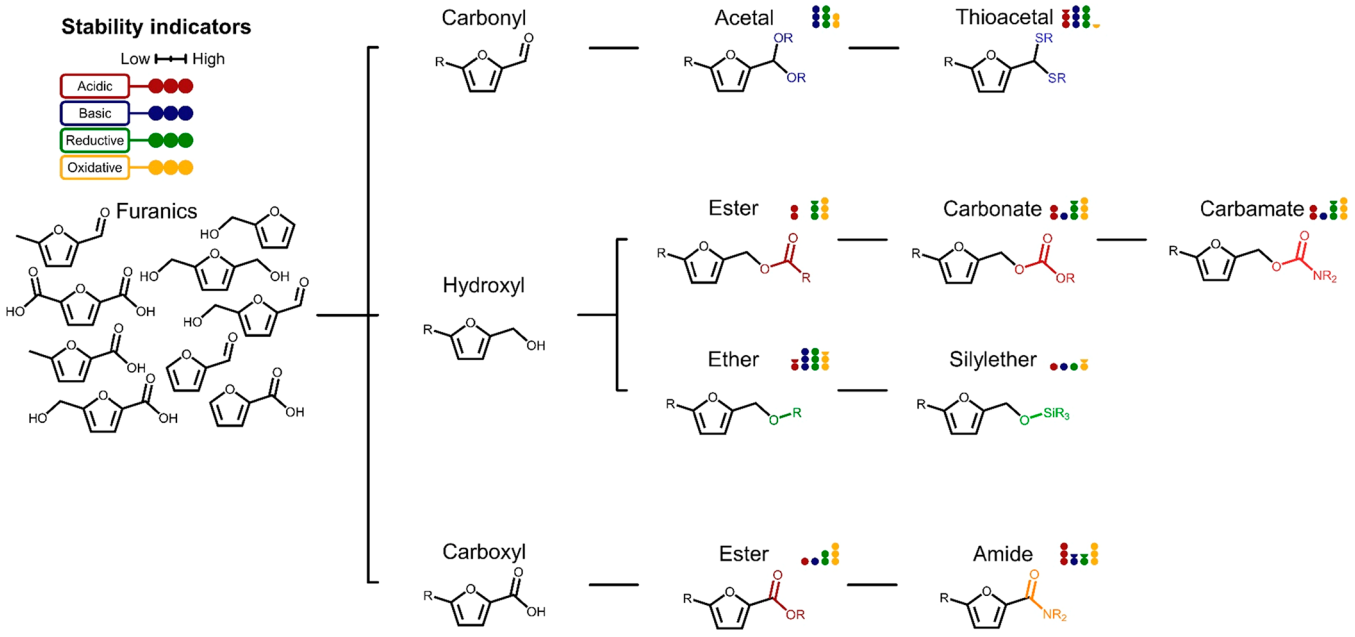

Figure 13. Selecting a suitable strategy relies on identifying the problematic functional group first, followed by choosing the correct protection group based on the reaction conditions. Stability indicators are based on the reactivity charts reported in Greene's Protective Groups in Organic Synthesis[41] and may differ from the actual stability of a protected furanic compound under these conditions.

nucleophilic addition of OH^- and subsequent elimination of the alkoxide (RO^-). Furthermore, reductive conditions can cleave the ester bond, although it can also be applied to convert the ester into other functional groups like hydroxyls or carbonyls.[69]

ALTERNATIVE STRATEGIES

Besides the main reaction routes, some alternative strategies are summarized in Figure 12. When the dehydration of fructose is carried out in the presence of HCl, 5-chloromethylfurfural (5-ClMF) is obtained rather than 5-HMF.[74,75] The direct chlorination of a hydroxyl-containing furanic can proceed as well, although the reaction must be operated at lower concentrations.[76] The chlorinated substrate can be used to obtain different furanic derivatives.[74] For example, 5-ClMF has been used in the synthesis of an HIV-1 capsid protein assembly[76] and of 5,5′-OBMF via the Williamson etherification method.[56,57] In theory, HCl can be recovered and reused for the nucleophilic substitution of OH group, making this a closed-loop process.

Another example is the silylation of 5-HMF, which was investigated for the synthesis of 2,5-diformylfuran (2,5-DFF).[77] Silyl ethers are popular protection groups due to their ease of removal in both acid and basic media.[51] Using trimethylsilyl chloride or *t*-butyldimethylsilyl chloride in combination with *N,N′*-DMF and imidazole catalysts, yields of 51% and 87%, respectively, of the corresponding silyl ether could be obtained (Figure 12). Subsequent oxidation was carried out in the presence of *N*-bromosuccimide (NBS) and azobis-(isobutyronitrile) (AIBN). Yields between 24% and 91% could be achieved depending on the selected reaction conditions.[77]

As stated in the Esterification section, 5-HMF is not often used as a hydroxy donor due to its propensity to oligomerization. However, when using an immobilized lipase B in the transesterification of 5-HMF with different acetates like ethyl acetate or dimethyl carbonate, yields between 80% and 92% of the corresponding ester could be achieved (Figure 12).[78] Even when short-chain carboxylic acids were employed, yields above 85% could be reported. However, initial concentrations in these experiments were low and the overall yield decreased upon increasing of the substrate loading. For example, with propionic acid, no ester formation was observed at high concentrations due the deactivation of the lipase under acidic conditions.[78] Separation of the ester and 5-HMF was achieved by using deep eutectic solvents (DES), and 80% of the furan ester could be recovered when using a DES of choline chloride and glycerol. Although these methods display promising results, most of procedures rely on the use of chlorinated solvents. Furthermore, the use of equimolar concentrations of inorganic reagents, leading to the formation of large waste streams, would in general limit the large-scale industrial implementation.

SELECTING A SUITABLE PROTECTION STRATEGY

In the previous section, examples of various protective strategies for the protection of 5-HMF have been discussed. Analyzing these methods reveals their applicability under different reaction conditions. Hence, selecting a proper strategy can be cumbersome, especially since this type of chemistry for furanic molecules is not fully developed yet. For synthetic organic chemistry, the use of reference books like *Greene's Protective Groups in Organic Synthesis*[51] is recommended to identify suitable protection groups and strategies. However, such databases often contain a plethora of examples and can therefore be overwhelming at first. Thus, simplifying the overall selection process could help in identifying appropriate strategies (Figure 13). In general, the problematic functional group (i.e., the hydroxyl or the carbonyl in 5-HMF, respectively) must be identified, followed by the evaluation of reaction conditions and possible catalysts. This will already significantly reduce the number of potential protection groups. Further considerations should entail the ease of the protection and deprotection as well as compliance to the green chemistry principles.[24,25] As can be deduced from the Etherification section, most protective strategies for 5-HMF already utilize potential biobased

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protecting agents. For example, acetalization procedures currently use 1,3-propanediol, which can be derived from the fermentation of sugars or hydrodeoxygenation of glycerol.[73,79] Also, both etherification and esterification procedures can benefit from naturally occurring alcohols, such as methanol and ethanol. Compliance to green chemistry principles is mostly hindered by the need for a solvent. However, the application of protection strategies allows the use of concentrated furanic solutions in the upstream processing.

As can be seen in Figure 13, having identified the problematic functional group, one might search for a suitable passivation method. For example, protection of the OH group via esterification or etherification is frequently applied. Ethers are stable under most conditions, although strong acidic environments might cleave the bond. Therefore, deprotection might be complicated as a low pH is required. As a result, etherification is mainly used to modify the properties of a furanic compound. In contrast to classic R-O-R bonds, silyl ethers (R_3-Si-O-R) might be more suitable passivating agents, although they were not studied extensively yet in conversion of furanics.[77] Especially, the cleavage of the silyl bond can be modulated by varying steric and electronic effects of the silyl group.[77,80] For example, the stability of the silyl ether increases with increasing size of the substituents (e.g., trimethylsilyl ether < triethylsilyl ether < triisopropylsilyl ether).[51]

In contrast to ethers, the application of esters (R-COO-R′) is very limited as it requires an additional carboxylic acid, which tends to be incompatible with the unprotected furanic compound (Figure 13). Transesterifications, on the other hand, could lower the risk of potential side reactions.[78] Esters can be easily cleaved under both basic and acidic conditions, while being stable in oxidative and neutral media. A carbonate group (R-OCOO-R′) is generally more stable, due to the resonance effect of the second oxygen and can therefore withstand much harsher conditions. Replacement of the second oxygen with a nitrogen, leading to the formation of a carbamate, improves the stability even more due to the enhanced resonance and H-bonding abilities.[81] Furthermore, carbamates are often introduced to improve the biocompatibility of pharmaceutical ingredients. Unfortunately, the synthesis of both carbonates and carbamates usually involve toxic reagents, like phosgene and chlorinated formamides.[51] Such dangerous compounds will subside the interest in carbonate and carbamate protection groups. The use of biocatalysts, alternatively, might in fact be a suitable alternative to synthesize esters with furanics as hydroxyl donors.[78] As discussed in the Etherification section, most esterifications start from (partially) oxidized 5-HMF that can subsequently be esterified via conventional methods (Figure 13). Similar to the carbonate/carbamate example, amides are intrinsically more stable due to enhanced electron resonance and H bonding. Consequently, the improved stability implies that more rigorous cleavage procedures are required (e.g., strong acidic or basic conditions).

In case the aldehyde functionality is the main bottleneck in the synthesis, few options are available for its passivation (Figure 13). So far, mainly acetals have been used because of their ease of formation. The stability of the acetal moiety can be tuned depending on the type of alcohol (mono-ol, diol, or triol). Cyclic acetals derived from polyols are generally more stable than their acyclic counterparts, and their overall stability is depending on the ring strain. For example, the six-membered ring, derived from 1,3-propanediol, proved to be more stable than the five-membered and the acyclic variety.[37] In general, acetalized furanic compounds are stable under basic and reductive conditions. However, often a buffer must be added to neutralize any *in situ* formed protons, which can cleave the acetal. When the reaction requires an acidic environment, thioacetals might be an interesting alternative to protect the carbonyl group.[82,83] In general, acid resistance increases with the amount of sulfur substitution (i.e., monoacetal < diacetal < monothioacetal < dithioacetal).[46] Thus far, studies concerning the thioacetalization of 5-HMF are rather scarce.[84,85] When different furanic compounds were investigated in the zeolite-catalyzed thioacetalization with ethyl-2-mercaptoacetate, yields above 90% could be reported for furfuraldehyde and 2-methylfurfuraldehyde.[84] For HMF, the thioacetal yield increased from 29% to 82% when only a small amount of 1-butyl-3-methylimidazolium chloride was added to the solution.

CONCLUSIONS

With the need for cleaner and more environmentally benign chemical building blocks, the potential of nonfood biomass as a suitable feedstock can no longer be ignored. Although the prospective of this renewable hydrocarbon source is enormous, actual industrial implementation is still limited. Problems arising during the storage and upgrading of reactive furanic compounds, like 5-HMF, necessitates the use of diluted furan solutions or mild reaction conditions to mitigate humin formation. In view of this, selective passivation of reactive functional groups is a viable means to raise the product selectivity. Although this type of chemistry is common practice in the field of fine chemical and pharmaceutical production, it is still relatively underdeveloped for biomass conversion. Selecting a proper protection strategy depends on several factors such as substrate type, reaction conditions, and desired products. The number of existing methods to passivate functional groups in furanic compounds is relatively low. Thus, many opportunities arise to investigate and develop novel protection methodologies for the conversion of reactive furanics. The example of 2,5-FDCA production from 5-HMF ethers involving catalysis, electrochemistry, and organic synthetic methods demonstrates the potential of combining different areas of expertise. Especially with regards to the green chemistry principles, the use of nontoxic and renewable reagents requires more attention. Nonetheless, chemical protection strategies might be interesting tools to bring forth the necessary product selectivity to facilitate the transition from a fossil-based industry toward the application of biorenewable building blocks.

AUTHOR INFORMATION

Corresponding Authors

Kiyotaka Nakajima − *Institute for Catalysis, Hokkaido University, Sapporo 0010021, Japan;* orcid.org/0000-0002-3774-3209; Email: nakajima@cat.hokudai.ac.jp

Emiel J. M. Hensen − *Laboratory of Inorganic Chemistry and Catalysis, Eindhoven University of Technology, 5600 MB, Eindhoven, The Netherlands;* orcid.org/0000-0002-9754-2417; Email: e.j.m.hensen@tue.nl

Authors

Ferdy J. A. G. Coumans − *Laboratory of Inorganic Chemistry and Catalysis, Eindhoven University of Technology, 5600 MB, Eindhoven, The Netherlands*

Zhanna Overchenko − *Laboratory of Inorganic Chemistry and Catalysis, Eindhoven University of Technology, 5600 MB, Eindhoven, The Netherlands*

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Jan J. Wiesfeld − *Institute for Catalysis, Hokkaido University, Sapporo 0010021, Japan*
Nikolay Kosinov − *Laboratory of Inorganic Chemistry and Catalysis, Eindhoven University of Technology, 5600 MB, Eindhoven, The Netherlands;* orcid.org/0000-0001-8520-4886

Complete contact information is available at: https://pubs.acs.org/10.1021/acssuschemeng.1c06723

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Ferdy J. A. G. Coumans has been working as a Ph.D. researcher in the Department of Chemical Engineering and Chemistry at Eindhoven University of Technology (The Netherlands) since January 2019, under the supervision of Prof. Emiel Hensen. His doctoral research is focused on the conversion of bioderived compounds towards chemical building blocks.

Zhanna Overchenko earned her Master's degree at Eindhoven University of Technology in 2021. Her Master's project was focused on transient analysis of zeolite catalysts in the methanol-to-hydrocarbons reaction under the supervision of Nikolay Kosinov and Emiel Hensen.

Jan J. Wiesfeld (Obbicht, The Netherlands, 1986) obtained his Ph.D. degree in 2019 from the Department of Chemical Engineering and Chemistry at Eindhoven University of Technology (The Netherlands) under the supervision of Prof. Emiel Hensen. He continued his research as a postdoctoral fellow at the Institute for Catalysis, Hokkaido University, in 2020. His current research is focused on the selective oxidation and valorization of biomass-derived compounds.

Nikolay Kosinov received a Master's degree from Novosibirsk State University, Russia, in 2010 and obtained a Ph.D. degree from Eindhoven University of Technology (TU/e), The Netherlands, in 2014. After several projects as a research associate at TU/e and TU Delft, he became an assistant professor at TU/e in 2018. His research is aimed at the synthesis, operando spectroscopy characterization, and application of heterogeneous catalytic materials as well as mechanistic understanding of their catalytic action. His main areas of interest include unconventional transformations of natural gas (methane) and CO_2 to value-added chemicals.

Kiyotaka Nakajima obtained his Ph.D. degree in 2006 from the Tokyo Institute of Technology. After a postdoctoral fellow in Toyota R&D

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Laboratories, Inc. (2006−2007) and assistant professor at the Materials and Structures Laboratory at the Tokyo Institute of Technology (2007−2015), he started working as an associate professor at the Institute for Catalysis, Hokkaido University, in 2015. The main focus of his current research is to design heterogeneous catalysts and catalytic reactions aiming for the valorization of biomass-derived cabohydrates to building blocks for commodity chemicals.

Emiel J. M. Hensen (Geleen, The Netherlands 1971), professor of inorganic materials and catalysis at Eindhoven University of Technology, has been carrying out research in heterogeneous catalysis for nearly two decades. He focuses on fundamental aspects of reaction mechanisms, combining operando characterization with theoretical modeling aiming at understanding the nature of active sites. He has published nearly 600 research papers and more than 10 book chapters and is an inventor of several patents. Dr. Hensen earned his M.Sc. and Ph.D. degrees at Eindhoven University of Technology under direction of Prof. Rutger van Santen and worked also at the University of Amsterdam, Hokkaido University, and Shell.

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■ ABBREVIATIONS

IPCC, International Panel on Climate Change; 5-HMF, 5-hydroxymethylfurfural; 2,5-DHH, 2,5-dioxo-6-hydroxyhexanal; FA, formic acid; LA, levulinic acid; 2,5-FDCA, 2,5-furandicarboxylic acid; 5-FFCA, 5-formylfurancarboxylic acid; PEF, polyethylene furanoate; 2,5-FDMC, 2,5-furandimethylcarboxylate; 2,5-FDHEC, 2,5-furandi-2-hydroxyethylcarboxylate; *N,N′*-DMF, *N,N′*-dimethylformamide; 2,5-BHMF, 2,5-bishydroxymethylfuran; 2,5-BHMTHF, 2,5-bishydroxymethyltetrahydrofuran; 5-ClMF, 5-chloromethylfurfural; *5,5′*-OBMF, *5,5′*-(oxy-bis(methylene))-bis-2-furfural; ZSM-5, Zeolite Socony Mobil-5; 5-AMF, 5-alkoxymethylfurfural; 2,5-DEMF, 2,5-diethoxymethylfurfural; 2,5-DFF, 2,5-diformylfuran; 5-HMFCA, 5-hydroxymethylfurancarboxylic acid; 2,5-FDCA, 2,5-furandicarboxylic acid; 1,4-TPA, 1,4-terephthalic acid; 1,4-DET, 1,4-diethylterephthalate; 2,5-DEF, 2,5-diethylfuranoate; DAC, Diels−Alder cycloaddition; 4-HMBA, 4-hydroxymethylbenzoic acid; M-5-MMMF, methyl-5-(methoxymethyl)-furanoate; M-4-MMB, methyl-4-(methoxymethyl)-benzoate; NBS, *N*-bromosuccimide; AIBN, azobis(isobutyronitrile); DES, deep eutectic solvents

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