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COMMUNICATION

Chemical-switching strategy for synthesis and controlled release of norcantharimides from a biomass-derived chemical

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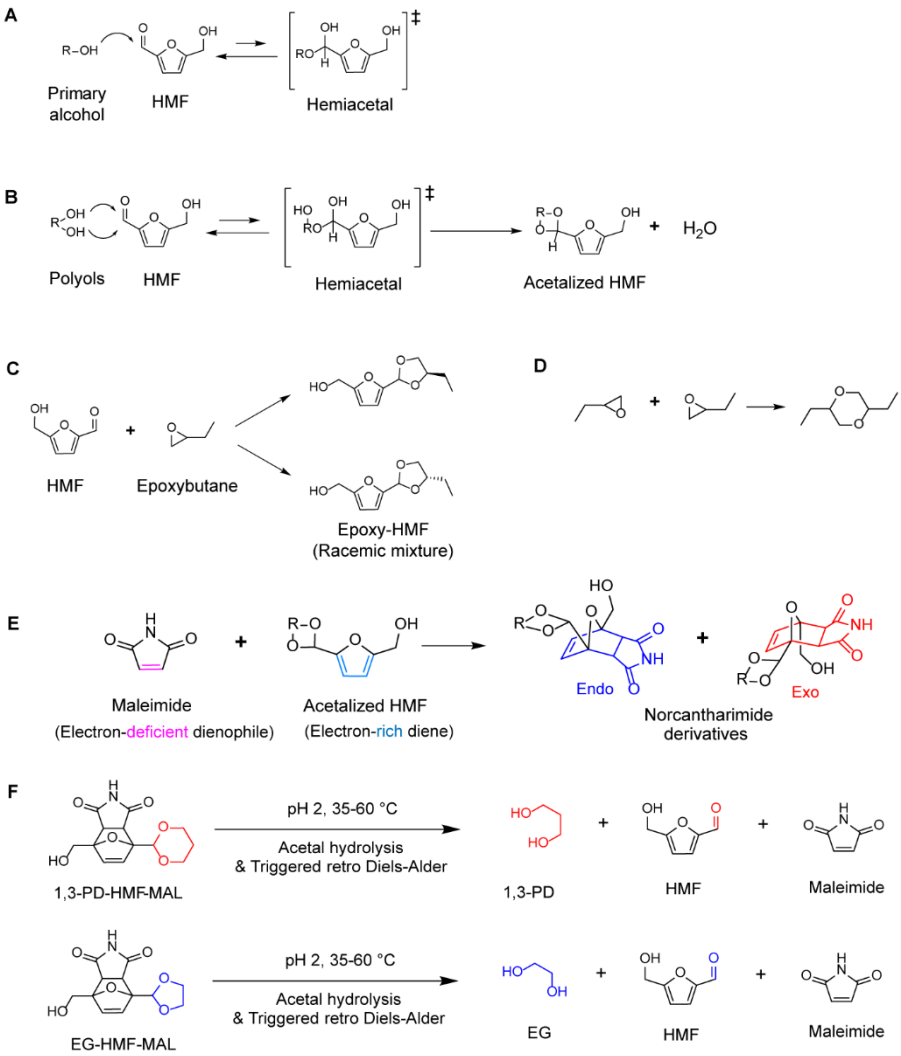
Abstract: We report catalytic strategies to synthesize and release chemicals for applications in fine chemicals, such as drugs and polymers from a biomass-derived chemical, 5-hydroxymethyl furfural (HMF). The combination of the diene and aldehyde functionalities in HMF enables catalytic production of acetalized HMF derivatives with diol or epoxy reactants to allow reversible synthesis of norcantharimide derivatives upon Diels-Alder reaction with maleimides. Reverse-conversion of the acetal group to an aldehyde yields mismatches of the molecular orbitals in norcantharimides to trigger retro Diels-Alder reaction at ambient temperatures and releases reactants from the coupled molecules under acidic conditions. These strategies provide for the facile synthesis and controlled release of high-value chemicals.

Introduction

Biomass conversion is a sustainable source of energy and chemicals, which can mitigate environmental concerns and produce high-value materials from non-edible plants[1,2]. Current trends in decreasing prices of transportation fuels and increasing importance of individual health treatment and environmental protection have created new opportunities for biomass conversion in pharmaceutical[3,4] and renewable polymer applications[5,6]. Synthesis and release of chemicals, which are of critical importance for fine chemicals, involve the following key chemical challenges: (i) designing a material that provides chemical bonding sites, (ii) incorporating a mechanism that releases the chemical at ambient temperatures, and (iii) controlling the release mechanism at the desired target. We show that all of these challenges can be fulfilled by the synthesis of materials containing a furan group conjugated to an aldehyde group, such as 5-hydroxymethylfurfural (HMF) that is effectively produced from biomass[7]. A key chemical property of HMF that has not been utilized previously[8] is this conjugation between the diene and aldehyde functionalities. In particular, the electron-withdrawing nature of aldehyde group inhibits the reactivity of diene group in HMF to undergo Diels-Alder reactions with dienophiles. However, by converting the aldehyde group in HMF to an electron-donating hydroxyl group, HMF can append maleimide-based chemicals through Diels-Alder coupling[9]. Maleimides, containing a dienophilic C=C bond and imide functionalities, have served as sites to append additional chemicals for the synthesis of therapeutic molecules, such as norcantharimides[10,11] and antibody-drug-conjugates[12,13], and for the production of novel polymers[14]. Moreover, acetalization of HMF not only produces an electron-rich diene for Diels-Alder reaction, but it also alters the reversibility of acetal formation and thereby allows for the controlled release of chemicals by hydrolysis[15,16]. Accordingly, the combination of acetalized HMF and maleimide provides a catalysis platform to control the synthesis and release of chemicals.

Herein, we synthesize various norcantharimide derivatives from biomass-derived HMF by acetalization over an acid catalyst, Amberlyst-15, followed by Diels-Alder reaction with maleimide. The norcantharimides release the starting materials by retro Diels-Alder reaction that is triggered by acetal hydrolysis under acidic (≤pH 3) conditions. The synergy of the furan and aldehyde functionalities in HMF thus enables the production of therapeutic and polymeric materials, and the controlled chemical release at ambient temperatures (35-60ºC). Scheme 1 describes reaction schemes for the synthesis and release of norcantharimide derivatives.



Scheme 1. Reaction pathways for acid-catalyzed HMF acetalization with **(A)** primary alcohols, **(B)** polyols, **(C)** epoxybutane, and **(D)** epoxybutane dimerization; **(E)** Diels-Alder reaction of maleimide and acetalized HMF; **(F)** Chemical release by acetal hydrolysis and triggered retro Diels-Alder reaction.

Results and Discussion

HMF acetalization with various alcohols (Scheme 1.A, B) was examined over Amberlyst-15 catalyst in tetrahydrofuran (THF) at 35ºC (Figure S9-S18, Table S1). None of the primary alcohols (Entry 1-4 in Table S1) reacted with HMF, whereas the acid catalyst facilitated HMF self-condensation (Entry 5 in Table S1, Figure S28). HMF self-condensation into humins occurred when the molar ratio of HMF to 1,3-propanediol (1,3-PD) was 1:1. In contrast, larger amounts of 1,3-PD (>2 equivalent diol to HMF) suppressed HMF self-condensation by increasing the reaction between 1,3-PD and HMF. Acetalization of HMF and 1,3-PD reached an equilibrium yield of 92%[17] within 3% error, after 4 h of reaction (Figure 1.A). The consumption of two reactants was equivalent at each reaction time, indicating the absence of side-reactions (Figure S1). The absence of side-reactions allows for characterization of feeds and products by assigning the chemical shifts in NMR spectra and thereby quantifying the conversion and yield. 1,3-propanediol derivatives with HMF (Entry 7,9,13 in Table S1) synthesized 6-member cyclic acetals in high yield (>93%). The electronegative sp^2 carbon in 2-methylene-1,3-propanediol (Entry 14 in Table S1) produced a less stable 6-member cyclic acetal in lower yield (66.7%). Low pentaerythritol (Entry 15 in Table S1) solubility in THF induced colloidal phase reaction and resulted in 66.7% yield. 55% product yields were achieved from ethylene glycol (EG) derivatives by producing 5-member cyclic acetals (Entry 6,8 in Table S1). Production of larger cyclic acetals (≥7-member ring), which have higher ring strain than 6-member ring, resulted in the lowest yield from 20.4% to 33.7% (Entry 10-12 in Table S1). These results demonstrate that the structural stability of cyclic acetals affects the product yield in acetalization. Furthermore, epoxybutane reacted with HMF to synthesize a 5-member cyclic acetal (Epoxy-HMF) in Scheme 1.C. Excess amounts of epoxybutane (8 equivalent epoxybutane to HMF) improved product yield up to 15.4% (Entry 5,9 in Table S2) with equivalent molar ratio of R- and S-diastereoisomer (Figure S19). However, a large excess of epoxybutane without THF solvent facilitated epoxybutane dimerization (Figure S29) as a side-reaction (Scheme 1.D) resulting in low (<6%) product yield (Entry 3,6 in Table S2). The entropy penalty of the bimolecular reaction explains the lower yield (15.4%) of 5-member cyclic acetal,

compared to the product yield (55.6%) from ethylene glycol reactant.

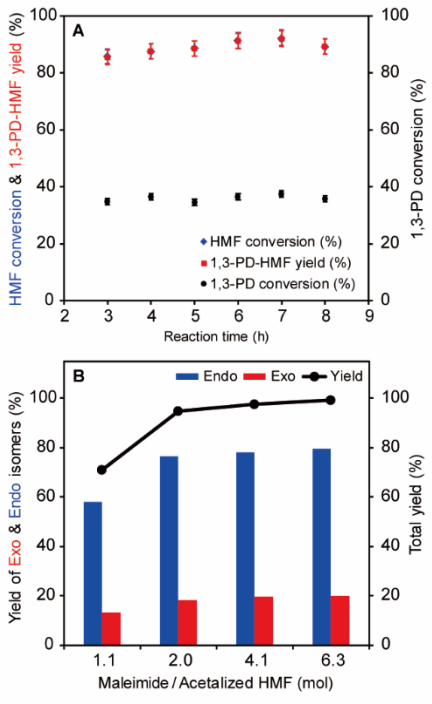
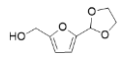
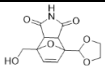
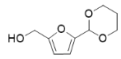
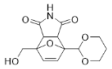
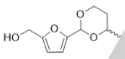
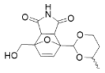
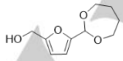
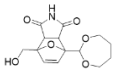
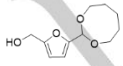
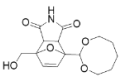
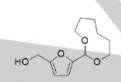
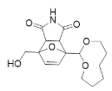
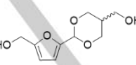
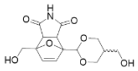
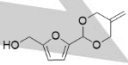
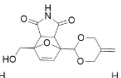
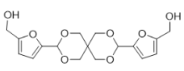
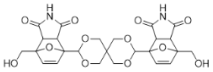


Figure 1. (A) HMF conversion, 1,3-PD conversion, and acetalized HMF (1,3-PD-HMF) yield at different reaction time, Error bar: ±3% deviation, HMF conversion and 1,3-PD-HMF yield are overlapped (Reaction conditions: 35ºC); **(B)** Yield of endo- and exo-1,3-PD-HMF-MAL (Reaction conditions: 50ºC, 67 h).

The acetalization of the aldehyde group in HMF provides an electron-rich diene and enables Diels-Alder reaction with maleimide (Scheme 1.E). The products were analyzed by NMR spectra (Figure S20-S27) because there was no side-reaction, such as degradations of HMF and maleimide, under the reaction conditions of Diels-Alder reaction (Figure S30). Figure 1.B shows that 2 equivalent maleimide to acetalized HMF resulted in high yield (94.7%) of the norcantharimide derivative (Entry 2 in Table 1). The highest yield (90.9-95.2%) was obtained from 6-member cyclic acetals (Entry 2,3,7,9 in Table 1). The electronegative sp^2 carbon induced a less stable cyclic acetal and contributed to lower (75.5%) product yield (Entry 8 in Table 1). Moreover, low yields (≤64.1%) of Diels-Alder products were produced from acetalized HMF derivatives that possessed larger ring strain than 6-member cyclic acetals (Entry 1,4,5,6 in Table 1). As a result, chemical properties of the cyclic acetals, such as ring stability and electronegativity, affect the formation of norcantharimide derivatives, but the molar ratio of endo- and exo-diastereoisomers remained constant (endo-: exo- = 4:1, Figure S21-S26). Endo-selective coupling by Diels-Alder reaction of furans and maleimides is consistent with previous literature[18]. The endo-isomer is kinetically preferred to the exo-isomer by aligning the diene and dienophile molecular orbitals. Sequential reactions of acetalization and Diels-Alder coupling can be used to synthesize a polymer[14]. HMF-Pentaerythritol-HMF (HPH) and bis-maleimide were soluble in THF, whereas the Diels-Alder polymer of two monomers precipitated in THF by forming a solid material during polymerization (Figure S6.D). The polymerized material had low solubility in various organic solvents (THF, methanol, acetone, chloroform). Oligomers smaller than pentamers (Mn≤1513 g·mol^{-1} and Mw≤1599 g·mol^{-1}) were dissolved in THF and characterized by GPC analysis (Figure S6.A) with polystyrene as a calibration standard (Figure S6.B).

Table 1. Product yields and reaction conditions of Diels-Alder reaction of acetalized HMF and maleimide (Solvent: THF, Product yields were measured by NMR in Figure S20-S27, Trace yields represent uncertain yield from NMR resolution limit).

Entry	Acetalized HMF feed	Malemide/Acetalized HMF (mol)	Temp. (℃)	Time (day)	Product Yield (%)	Product structure
1		2.3	50	3	64.1	
2		2.0	50	3	94.7	
3		2.2	50	3	93.5	
4		2.2	50	3	50.0	
5		2.3	50	3	Trace (~21.7)	
6		2.3	50	3	Trace (~33.3)	
7		2.2	50	3	95.2	
8		2.3	50	3	75.5	
9		2.3	50	3	90.9	

Hydrolysis of the acetal group triggers molecular orbital mismatch in Diels-Alder coupled chemicals. Therefore, retro Diels-Alder reaction that is typically achieved by increasing the temperature can be triggered by acid-catalyzed acetal hydrolysis at constant temperature (Scheme 1.F and Figure S8.C). The effect of pH on the release rate was investigated using a 6-member cyclic acetal (1,3-PD-HMF-MAL) at 50ºC (Figure 2.A, B). Exo-isomer was synthesized in the reaction system because exo-1,3-PD-HMF-MAL was thermodynamically the most stable chemical in the system (Figure S5.B). The rate constants were measured by tracking the concentration of endo-isomer in different pH (Figure S4). By decreasing pH from 3 to 2, the rate constant increased from $4.36 \cdot 10^{-5}$ to $9.84 \cdot 10^{-5}$ $M^{-1}s^{-1}$ at 50°C. At higher pH conditions, the rate of acetal hydrolysis decreased and side-reactions, such as maleimide degradation became more important. In pH 4 and 5 buffers, competition between acetal hydrolysis, chemical degradation, and Diels-Alder reaction resulted in fluctuations of chemical concentrations (Figure S2). The triggered retro Diel-Alder reaction and degradations of maleimide and HMF in the chemical release system are independent reaction pathways that resulted from acid-catalyzed hydrolysis. Accordingly, tracking the concentration of each chemical in the feed and product solutions allows for investigation of these parallel reactions.

Furthermore, the 5- and 6-member cyclic acetals (Scheme 1.F) were used to compare the structural and/or thermodynamic stability effect on the reaction kinetics of chemical release at 35, 50, and 60ºC in pH 2 buffer. Activation energies of endo-1,3-PD-HMF-MAL, endo-EG-HMF-MAL, and exo-EG-HMF-MAL were measured to be 108, 92, and 86 $kJ \cdot mol^{-1}$, respectively (Figure S5.A). The activation energies of triggered retro Diels-Alder reaction are lower than that of thermal retro Diels-Alder reaction (157 $kJ \cdot mol^{-1}$) of a previously reported furan-maleimide adduct[18]. By comparison of exo- and endo-isomers, a lower activation energy (86 $kJ \cdot mol^{-1}$) of exo-EG-HMF-MAL than endo-counterpart (92 $kJ \cdot mol^{-1}$) results from thermodynamic stability of exo-conformation (Figure S5.C). A similar comparison of 5- and 6-member cyclic acetals shows that a lower structural stability of EG-HMF-MAL (5-member ring) contributes to lower activation energy than 1,3-PD-HMF-MAL (6-member ring) and accelerates chemical release rate (Figure S5.B, C). 21.9% of 1,3-PD-HMF-MAL, including endo-isomer decomposition and exo-isomer formation, was decoupled after 32.5 h, while 42.7% of EG-HMF-MAL was hydrolyzed after 20 h (Figure S3).

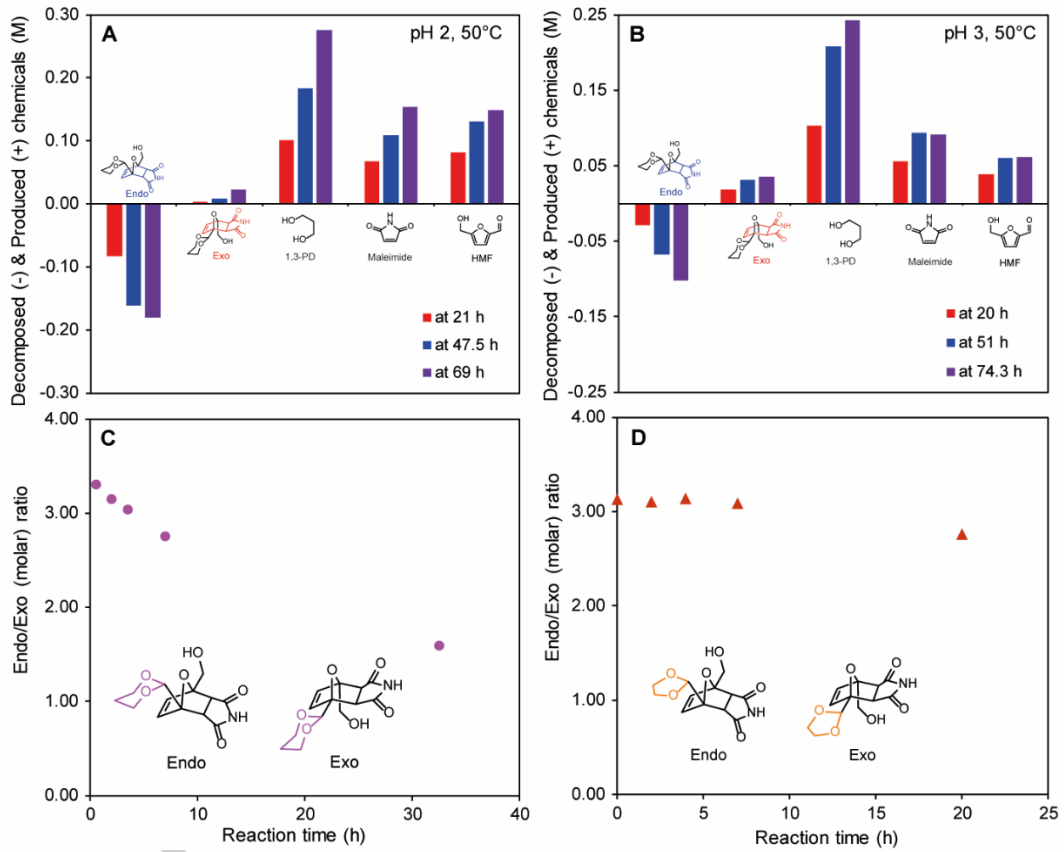


Figure 2. Concentrations of consumed (-) and produced (+) chemicals versus time by chemical release of 1,3-PD-HMF-MAL solution in **(A)** pH 2, **(B)** pH 3 acetate buffer at 50°C (Initial chemical concentrations of (**A**) were endo-, exo-, 1,3-PD, malemide, HMF were 0.62, 0.19, 0.66, 0.54, 0.00 M, respectively; Initial chemical concentrations of (**B**) were endo-, exo-, 1,3-PD, malemide, HMF were 0.56, 0.18, 0.74, 0.64, 0.07 M, respectively); Molar ratio of diastereoisomers versus time in **(C)** 1,3-PD-HMF-MAL, and **(D)** EG-HMF-MAL solution in pH 2 acetate buffer at 60ºC. (Concentration of endo- and exo-isomers were measured by HPLC).

The molar ratio of diastereoisomers decreased by acetal hydrolysis in 1,3-PD-HMF-MAL solution due to the decomposition of endo-isomer and the formation of exo-isomer (Figure 2.C). Meanwhile, similar hydrolysis rate constants of endo- and exo-EG-HMF-MAL (k_{endo}=$4.27 \cdot 10^{-4}$ $M^{-1} \cdot s^{-1}$ and k_{exo}=$4.07 \cdot 10^{-4}$ $M^{-1} \cdot s^{-1}$ in Figure S5.A) maintained the diastereoisomers ratio constant during the reaction (Figure 2.D). The difference of diastereoisomer ratio in feed, measured by HPLC (endo/exo=3.3)

and by NMR (endo/exo=4.0), resulted from the overlap of the isomers peaks in HPLC analysis (Figure S8), and it underestimated concentrations of endo- and exo-compounds in Figure 2.A and B.

Conclusions

Biomass-derived HMF can be utilized as a catalytic platform for facile synthesis and release of high-value chemicals, such as norcantharimide derivatives. Acid-catalyzed acetalization of HMF activates a 'chemical-switch' and enables Diels-Alder reaction by converting the electron-withdrawing aldehyde to an electron-donating acetal. As the chemical stabilities of the cyclic acetals increase, the yields of desired products by acetalization and Diels-Alder reaction increase. Then, hydrolysis of the acetal linkage can be employed to turn off the 'chemical-switch' in the Diels-Alder coupled molecules and trigger the release of starting materials at ambient temperatures (35-60ºC). At low pH (≤pH 3) conditions, chemical release from norcantharimides can be achieved at constant temperature, whereas chemical release is suppressed at higher pH (≥pH 4) conditions. The controlled chemical release at 35ºC implies that this release strategy could be utilized in drug delivery systems at human body temperature. For example, the diol groups in HMF-Pentaerythritol-HMF monomers can be reacted with terephthalic acids to produce solid polyesters[6], and the coupling of the furan groups to maleimides (Entry 9 in Table 1) could serve as a maleimide-based drug carrier.

Experimental Section

Materials. The following materials were used in all experiments: 5-(hydroxymethyl) furfural (HMF, AK Scientific, 98%), Maleimide (99%, Sigma-Aldrich), Bis-maleimide (95%, Sigma-Aldrich), Tetrahydrofuran (THF, Sigma-Aldrich), Dichloromethane (Sigma-Aldrich, anhydrous 99.8%), Amberlyst-15 (Sigma-Aldrich), Methanol (Fisher Scientific, 99.9% HPLC grade), Ethanol (Sigma-Aldrich, anhydrous, 99.5%), Phenol (Sigma-Aldrich, >99%), N-(2-Hydroxyethyl)maleimide (Sigma-Aldrich, 97%), Ethylene glycol (EG, Sigma-Aldrich), 1,3-propanediol (1,3-PD, Sigma-Aldrich, 98%), Glycerol (Sigma-Aldrich), 1,3-butanediol (Sigma-Aldrich), 1,4-butanediol (Sigma-Aldrich), 1,5-pentanediol (Sigma-Aldrich, 96%), 1,6-hexanediol (Sigma-Aldrich, 99%), 2-Methylene-1,3-propanediol (Sigma-Aldrich, 97%), 2-Hydroxymethyl-1,3-propanediol (Sigma-Aldrich, 97%), Pentaerythritol (Sigma-Aldrich, 99%), 1,2-Epoxybutane (Sigma-Aldrich, 99%), Acetic acid (Sigma-Aldrich, >99%), Sodium acetate (Sigma-Aldrich, >99%), HCl (6N, Fisher Scientific), Acetone-d_6 (ACROS organic, for NMR 99.8 atom% D), Methanol-d_4 (ACROS organic, for NMR 99.8 atom% D), Chloroform-d ($CDCl_3$, Sigma-Aldrich, for NMR 99.8 atom% D), Mesitylene (Alfa Aesar, >98%), and Mill-Q water (~18 MΩ cm).

HPLC analysis of hydrolyzed solutions. The chemical concentrations of hydrolyzed solutions were quantified by high performance liquid chromatography (HPLC) analysis. 0.054 g of feed solutions of 5- and 6-member cyclic acetal compounds and the hydrolyzed solutions were diluted in 0.449 g of Milli-Q water (10 times dilution by volume) for analyzing the concentrations of cyclic acetal compounds, diols, maleimide, and HMF. All diluted samples were filtered through 0.2 µm PTFE filter before the sample was injected into the HPLC. The concentrations of fructose, sugar isomers, and acidic by-products were measured by a Water 2695 separation module equipped with an Aminex HPX-87H (Bio-Rad) column and RI detector, while the HMF concentration was measured with a Waters 2998 PDA detector at 320 nm. The temperature of the HPLC column was maintained at 65ºC, and the flow rate of the mobile phase (pH 2 water, acidified by sulfuric acid) was 0.6 mL. For calibration of concentrations by HPLC analysis, the controlled amounts of commercial HMF, maleimide, ethylene glycol, and 1,3-propanediol were dissolved in Milli-Q water to prepare standard chemicals for calibration curves. Cyclic acetals were synthesized by the following methods and separated by HPLC to prepare calibration curves. HPLC calibration curves for the standard chemicals are illustrated in Figure S7.

GPC analysis of Diels-Alder oligomers. Gel permeation chromatography (GPC) analysis was performed by using a Viscotek GPCmax/VE 2001 instrument fitted with PolyPore columns (2×300×7.5 mm) featuring 5 µm particle size from Polymer Laboratories. Liquid solution, containing the Diels-Alder oligomers in THF, was eluted with THF at a flow rate of 1 mL·min^{-1} at 40°C. The molecular weights of the oligomers were characterized by UV (at 390 nm wavelength) detection using a Viscotek Model 302-050 Tetra Detector Array. Omnisec software (Viscotek, Inc.) was used for data processing such as positioning the baseline, setting limits, and applying the molecular weight calibration.

NMR analysis of acetalized HMF and norcantharimide derivatives samples. ^{1}H Nuclear magnetic resonance (NMR) and ^{13}C NMR spectrum were obtained by using Brucker Avance-500 spectrometer. Tetramethylsilane (TMS) (δ: 0 ppm) was used as a reference for chemical shifts.

Time dependent acid-catalyzed acetalization of HMF and 1,3-propanediol (1,3-PD). 0.100 g of HMF (0.8 mmol), 0.149 g of 1,3-propanediol (1,3-PD, 2.0 mmol), and 1.115 g (1.25 mL) of THF solvent were mixed in a glass vial, and 0.050 g of ground Amberlyst-15 (0.2 mmol acid site, particle size 40-150 µm) was added in the glass vial to prepare the feed samples. The feed samples were placed at 35ºC in oil bath for controlled reaction times (3,4,5,6,7, 8 h). A cross-shaped magnetic stir bar was used for mixing each sample at 750 rpm during the reaction. After the controlled reaction time, Amberlyst-15 catalyst was filtered from the sample solution by 0.2 µm PTFE filter. THF solvent of the filtered solution was evaporated at 40ºC, for >15 min, under <50 mbar. 0.20 g of the evaporated sample was dissolved in 0.66 g of chloroform-d ($CDCl_3$) solvent with 0.03 g of mesitylene as an internal standard to prepare NMR sample. ^{1}H NMR and ^{13}C qNMR spectrum were used for chemical characterization and calculating the conversion and yield.

Acid-catalyzed acetalization of HMF and various alcohols. 0.100 g of HMF (0.8 mmol), controlled amounts of various alcohols (Alcohol/HMF (mol) ratio ≈ 2, Entry 1-14 in Table S1), and 1.12 g (1.25 mL) of THF solvent (or 1.66 g (1.25 mL) of dichloromethane solvent, for Entry 5 in Table S1) were mixed in a glass vial, and 0.050 g of Amberlyst-15 (particle size 40-150 µm) was added in the vial to prepare the feed samples. For synthesis of Entry 15 in Table S1, 0.100 g of HMF, 0.054 g of pentaerythritol (Pentaerythritol/HMF (mol) = 0.5), and 5 g (5.6 mL) of THF solvent were mixed in a glass vial (colloidal phase solution), and 0.050 g of Amberlyst-15 was added in the vial to prepare the feed sample. The feed samples were placed at 35ºC in oil bath for > 4 h (Table S1). A cross-shaped magnetic stir bar was used for mixing each sample at 750 rpm during the reaction. After the controlled reaction time, Amberlyst-15 catalyst was filtered from the sample solution by 0.2 µm PTFE filter. THF or dichloromethane solvent of the filtered solution was evaporated at 40ºC, for >15 min, under <50 mbar. Small amounts (>0.04 g) of the evaporated sample were dissolved in 0.66 g of chloroform-d ($CDCl_3$) solvent for ^{1}H NMR and ^{13}C qNMR analysis to characterize the chemicals and calculate the conversion and yield.

Acid-catalyzed acetalization of HMF and epoxybutane. For Entry 5 in Table S2 (the best yield of Epoxy-HMF), 0.100 g of HMF (0.8 mmol), 0.458 g of epoxybutane (6.4 mmol), and 1.11 g (1.24 mL) of THF solvent were mixed in a glass vial, and 0.050 g of

Amberlyst-15 (particle size 40-150 μm) was added in the vial to prepare the feed sample. For the solvent system without THF (Entry 6 in Table S2), 0.100 g of HMF (0.8 mmol) and 1.032 g (1.24 mL) of epoxybutane (14.3 mmol) were mixed in a glass vial, and 0.050 g of Amberlyst-15 was added in the vial to prepare the feed sample. The feed samples were placed at 35ºC in oil bath for 15.5 h. A cross-shaped magnetic stir bar was used for mixing each sample at 750 rpm during the reaction. After the controlled reaction time, Amberlyst-15 catalyst was filtered from the sample solutions by 0.2 μm PTFE filter. THF solvent and/or unreacted epoxybutane of the filtered solution were evaporated at 40ºC, for >25 min, under <50 mbar. 0.10 g of the evaporated sample was dissolved in 0.63 g of chloroform-d ($CDCl_3$) solvent and analyzed by ^{1}H NMR and ^{13}C qNMR spectrum.

Molar ratio effect of 1,3-PD-HMF and maleimide on Diels-Alder reaction . For preparation of 1,3-PD-HMF solution, 0.10 g of HMF, 0.15 g of 1,3-PD and 1.12 g of THF solvent were mixed, and 0.05 g of Amberlyst-15 (particle size 40-150 μm) was added as acid-catalyst for 4 h at 35ºC. After acetalization, Amberlyst-15 was filtered by 0.2 μm PTFE filter for 1,3-PD-HMF solution (95 % HMF conversion to 1,3-PD-HMF by NMR analysis). Feed solutions for Diels-Alder reaction were prepared by mixing 1.06 g of the 1,3-PD-HMF solutions and the controlled amounts (0.059 g, 0.118 g, 0.235 g, 0.362 g) of maleimide. The feed solutions were placed at 50ºC in oil bath for 67 h. A cross-shaped magnetic stir bar was used for mixing each sample at 750 rpm during the reaction. THF solvent was evaporated at 40ºC, for >15 min, under <50 mbar. Small amounts (>0.03 g) of the evaporated sample were dissolved in 0.74 g of chloroform-d ($CDCl_3$) solvent for ^{1}H NMR and ^{13}C qNMR analysis to characterize the chemicals and calculate the conversion and yield.

Diels-Alder reaction of various acetalized HMF and maleimide. Feed solutions were prepared by following the method in Table S1, and detailed feed conditions are described in Table S3. The feed solutions were placed at 50ºC in oil bath for 3 days (~67 h). A cross-shaped magnetic stir bar was used for mixing each sample at 750 rpm during the reaction. THF solvent was evaporated at 40ºC, for >15 min, under <50 mbar. Small amounts (>0.03 g) of the evaporated sample were dissolved in chloroform-d (or acetone-d_6) solvent for ^{1}H NMR and ^{13}C qNMR analysis to characterize the chemicals and calculate the conversion and yield. In Table S3, moles of various acetalized HMF in the acetalized HMF solution were calculated by the HMF conversion from NMR analysis.

Diels-Alder polymerization of HMF-Pentaerythritol-HMF (HPH) and bis-maleimide. The feed solution for synthesis of HPH monomer was prepared by mixing 0.40 g of HMF, 0.21 g of pentaerythritol, and 19.7 g of THF solvent. 0.20 g of Amberlyst-15(particle size 40-150 μm) catalyst was added into the feed solution. HPH monomer solution was synthesized after 17 h reaction at 35ºC in an oil bath. 0.54 g of bis-maleimide and 3.4 g of THF were added into the HPH monomer solution to completely dissolve bis-maleimide in the solution. The homogeneous solution, containing HPH and bis-maleimide, was placed at 50ºC in an oil bath for 11 days and stirred at 750 rpm until yellow precipitates appeared. A liquid phase of the polymerized solution was separated from the solid precipitates to be analyzed by GPC. 6.83 g of THF was used to re-disperse the solid material by sonication to wash impurities. 0.03 g of the washed polymer material was mixed with 0.5 mL of NMR solvents (acetone-d_6, methanol-d_4, chloroform-d), and the samples were analyzed by NMR to examine the solubility. NMR spectrum showed that no polymer was dissolved in NMR solvents.

pH dependent acetal hydrolysis-triggered retro Diels-Alder reaction (chemical release). pH 5 acetate buffer solution was prepared by mixing 0.058 g of sodium acetate (0.7 mmol), 0.021 g of acetic acid (0.3 mmol) in 7.992 g (8 mL) of Milli-Q water. 6N HCl solution was diluted by Milli-Q water to prepare 3N HCl solution. Then, the controlled amount of 3N HCl solution was added to the pH 5 acetate buffer to prepare different pH buffer solutions (pH 2, 3, 4). A pH meter was used for monitoring pH of the acetate buffer solution. 1,3-PD-HMF-MAL (or 6-member cyclic acetal compounds) solution was prepared by the aforementioned method and Table S3. The 1,3-PD-HMF-MAL solution was evaporated at 40ºC, for 60 min, under <30 mbar to remove THF solvent and prepare the dried sample. For preparation of feed samples, 0.17 g of the dried sample and 0.4 g (0.4 mL) of acetate buffer with different pH (pH 2,3,4,5) were mixed in a glass vial (30 wt% dried sample in buffer). Each feed sample was placed at 35ºC (for Figure S8.C) or 50ºC (for Figure 2 and S2) in an oil bath for the chemical release reactions. The chemical concentrations in the feed and the hydrolyzed solutions were analyzed by HPLC.

Rate constant calculation of chemical release reactions. The dried samples of 1,3-PD-HMF-MAL and EG-HMF-MAL (see aforementioned method and Table S3) were dissolved in pH 2, and pH 3 acetate buffer. The concentrations of dried samples were 30 wt% in the acetate buffers and the sample solutions were reacted at 35, 50, 60ºC in an oil bath to measure the rate constants. Chemical concentrations were analyzed by HPLC, and the concentrations at low (<25%) conversion of endo-1,3-PD-HMF-MAL, endo-EG-HMF-MAL, and exo-EG-HMF-MAL in different pH conditions were used to measure the slope of the concentration profiles. Rate constants were calculated by equation (1).

$$k = \frac{-1}{[A]_0[B]_0} \cdot \left.\frac{d[A]}{dt}\right|_{t=0}$$ (where, $[A]_0$: initial molar concentration of endo- or exo-isomer, $[B]_0$: initial molar concentration of water (=55.6 M), $\left.\frac{d[A]}{dt}\right|_{t=0}$: slope of the concentration profile at low (<25%) conversion) ··· (1)

The rate constants were used for estimating activation energies of 5- and 6-member cyclic acetal compounds (Figure S5.A).

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[1] J. C. Serrano-Ruiz, R. M. West, J. A. Dumesic, *Annu. Rev. Chem. Biomol. Eng.* **2010**, *1*, 79–100.

[2] J. N. Chheda, G. W. Huber, J. A. Dumesic, *Angew. Chem. Int. Ed.* **2007**, *46*, 7164–7183.

[3] Z. Zuo, D. W. C. Macmillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260.

[4] W. Deng et al., see Supporting information. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 5093–5098.

[5] H. Chang, A. H. Motagamwala, G. W. Huber, J. A. Dumesic, *Green Chem.* **2019**, *21*, 5532–5540.

[6] N. Warlin et al., see Supporting information. *Green Chem.* **2019**, *21*, 6667–6684.

[7] A. H. Motagamwala, K. Huang, C. T. Maravelias, J. A. Dumesic, *Energy Environ. Sci.* **2019**, *12*, 2212–2222.

[8] W. Fan, C. Verrier, Y. Queneau, F. Popowycz, *Curr. Org. Synth.* **2019**, *16*, 583–614.

[9] K. Galkin, F. Kucherov, O. Markov, K. Egorova, A. Posvyatenko, V. Ananikov, *Molecules* **2017**, *22*, 2210.

[10] S. S. Cheng, Y. Shi, X. N. Ma, D. X. Xing, L. D. Liu, Y. Liu, Y. X. Zhao, Q. C. Sui, X. J. Tan, *J. Mol. Struct.* **2016**, *1115*, 228–240.

[11] C. E. Puerto Galvis, L. Y. Vargas Méndez, V. V. Kouznetsov, *Chem. Biol. Drug Des.* **2013**, *82*, 477–499.

[12] R. J. Christie, R. Fleming, B. Bezabeh, R. Woods, S. Mao, J. Harper, A. Joseph, Q. Wang, Z. Q. Xu, H. Wu, C. Gao, N. Dimasi, *J. Control. Release* **2015**, *220*, 660–670.

[13] R. P. Lyon, J. R. Setter, T. D. Bovee, S. O. Doronina, J. H. Hunter, M. E. Anderson, C. L. Balasubramanian, S. M. Duniho, C. I. Leiske, F. Li, P. D. Senter, *Nat. Biotechnol.* **2014**, *32*, 1059–1062.

[14] C. Goussé, A. Gandini, *Polym. Int.* **1999**, *48*, 723–731.

[15] E. R. Gillies, J. M. J. Fréchet, *Chem. Commun.* **2003**, *3*, 1640–1641.

[16] A. Schlossbauer, C. Dohmen, D. Schaffert, E. Wagner, T. Bein, *Angew. Chem. Int. Ed.* **2011**, *50*, 6828–6830.

[17] M. Kim, Y. Su, A. Fukuoka, E. J. M. Hensen, K. Nakajima, *Angew. Chem. Int. Ed.* **2018**, *57*, 8235–8239.

[18] V. Froidevaux, M. Borne, E. Laborbe, R. Auvergne, A. Gandini, B. Boutevin, *RSC Adv.* **2015**, *5*, 37742–37754.

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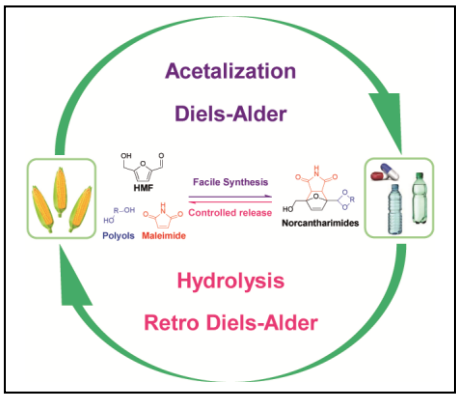
Entry for the Table of Contents



Biomass-derived 5-hydroxymethyl furfural (HMF) is utilized as a catalytic platform for facile synthesis and release of high-value chemicals that can serve as therapeutic ingredients and/or polymeric materials. Acetalization and hydrolysis of the aldehyde group in HMF can be used to control the reactivity of the diene functionality for the Diels-Alder reaction. The combination of aldehyde and diene in HMF, thus, acts as a 'chemical-switch'.