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Role of Lewis and Brønsted acidity in metal chloride catalysis in organic media: Reductive etherification of furanics

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ABSTRACT

Metal chlorides are demonstrated to behave as bifunctional acid catalysts in organic media in the one-pot reductive etherification of 5-hydroxymethylfurfural (HMF) in 2-propanol toward production of biodiesel. Two competing reaction pathways, direct etherification to 5-(isopropoxymethyl)furfural and reductive etherification to 2,5-bis(alkoxymethyl)furan, are proposed with the selectivity depending on the metal ion. Furfural and furfuryl alcohol are used as model compounds to investigate each pathway individually. The roles of Lewis/Brønsted acidity of metal chlorides solution are elucidated by kinetic studies in conjunction with salt speciation using electrospray soft ionization mass spectrometer. Brønsted acidic species, generated from alcoholysis of the metal chlorides, are the predominant catalytically active species in etherification. On the other hand, partially hydrolyzed metal cations produced by alcoholysis/hydrolysis are responsible Lewis acid centers for furfural reduction to furfuryl alcohol. Isotopic labeling experiments, in combination with GCMS and ¹HNMR analysis, reveal an intermolecular hydrogen transfer from the α-C of 2-propanol to the α-C of furfural as the rate-limiting step of furfural hydrogenation.

Keywords: reductive etherification, 5-hydroxymethyl furfural, furfuryl alcohol, furfural, metal chloride

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INTRODUCTION

Research on renewable production of fuels has drawn significant attention due to rising concerns about climate change. Lignocellulosic biomass, the most natural abundant source of carbon, offers a green alternative to fuels without interfering with human-food consumption.¹ Biomass-derived furanyl ethers possess high cetane number, high energy density, and proven performance when blended with petroleum-derived diesel.²⁻³ Such ethers can be synthesized from 5-hydroxymethyl furfural (HMF),⁴ a biomass derived platform chemical. HMF can be directly etherified by condensation with an alcohol to form 5-(alkoxymethyl)furfural (mono-ether)⁵⁻⁷, or after hydrogenation of its carbonyl group followed by etherification to form 2,5-bis(alkoxymethyl)furan (di-ether), i.e., a reductive etherification route.^{3, 8-9} The di-ether is higher grade fuel than the mono-ether owing to its higher stability and miscibility with commercial diesel.^{3, 9} While acid-catalyzed etherification of HMF to a mono-ether with ion exchange resins,^{3, 10-11} heteropolyacids,¹² aluminosilicates,^{7, 13} mineral acid,^{3, 13} and metal salts¹⁴⁻¹⁸ as catalysts has been studied quite extensively, literature on synthesis of the di-ether is limited. Bell and coworkers reported up to 60% yield to di-ether in a cascade reaction under H₂ pressure using a physical mixture of Pt/Al₂O₃ and Amberlyst-15.³ More recently, Jae et al. and Lewis et al. independently investigated the use of metal-substituted BEA zeolites for the one-pot synthesis of the di-ether in 2-propanol or ethanol, without H₂ gas.⁸⁻⁹ In this route, the Lewis acids are hypothesized to facilitate catalytic transfer hydrogenation of HMF by the Meerwein-Ponndorf-Verley (MPV) reduction in alcohol solvent that is also acting as a hydrogen donor. The product of the MPV reduction is sequentially etherified to the maximum of ca. 80% di-ether yield.⁸⁻⁹ Di-ether formation was also reported over metal oxide catalysts.¹⁹⁻

²⁰ Evidently, reductive etherification of HMF is a promising process for production of di-ether on account of several advantages: single catalyst, no H₂ gas required, and one-pot reactor for process efficiency.

Besides metal substituted BEA zeolites, whose synthesis is still rather challenging, conventional homogeneous Lewis acid metal chlorides (e.g., CrCl₃, AlCl₃) have been shown to be effective for intramolecular MPV reduction of aldose to ketose (e.g., glucose isomerization).²¹⁻²⁶ Mechanistic studies have revealed that the active-site structures of Sn-BEA and metal chlorides share striking similarities and facilitate the same catalytic pathways in aqueous solution.^{22-23, 27-31} In the chelated transition state, characteristic of MPV reduction, the metal center coordinates the O1 and O2 atoms of the aldose (e.g., glucose) during an intramolecular hydride shift from the C2 to the C1 carbon. Because of the analogies between zeolites and metal salts for isomerization of glucose, one might speculate on the potential activity of metal salts for reductive etherification of HMF. In addition, metal salts offer promising reusability as they are shown to be effectively recyclable after multiple runs without significant activity loss for glucose isomerization/dehydration to HMF.³²⁻³³

Although metal salts have been demonstrated to be effective catalysts for direct etherification of HMF to mono-ether in alcohol solvent¹⁴⁻¹⁶, no di-ether production has been reported. Our group previously investigated catalysis of furfural hydrogenolysis by metal chlorides in 2-propanol, and observed formation of isopropyl furfuryl ether.³⁴ However, that work focused on synthesis of methyl furan and did not further explore the potential for reductive etherification.

Herein, we assess the catalytic activity of inexpensive, conventional Lewis acid metal chlorides for the tandem reductive etherification of HMF in 2-propanol, and reveal two main reaction pathways, depending on the metal cation. Furfuryl alcohol (FA) and furfural are employed as model compounds to further investigate each of the two pathways independently. By correlating the metal chloride speciation and reaction kinetics, we demonstrate that the metal chlorides actually play a bifunctional role in the reductive etherification of furanic compounds in organic media.

EXPERIMENTAL METHODS

Materials

All chemicals and solvents were purchased from Sigma Aldrich and used without further modification. Reactants are HMF, furfural, and FA. The catalysts include ZnCl_2 , $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{YbCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{DyCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, and $\text{YCl}_3 \cdot 6\text{H}_2\text{O}$ as well as 0.1 M HCl in 2-propanol. Deuterated solvents for isotopic labeling experiments are 2-propanol- d_8 ($(\text{CD}_3)_2\text{CDOD}$) and 2-propanol-OD ($(\text{CH}_3)_2\text{CHOD}$).

Reductive etherification experiments

A typical experiment was carried out in a 100 mL Parr reactor vessel, consisting of 70 mL of 2-propanol solution of a metal salt and the reactant (HMF or furfural), sealed with 20 bar N_2 . The reactor was heated to the desired temperature in a customized band heater, using a temperature controller. Samples were taken periodically and filtered for post reaction analysis.

Etherification kinetic experiments

Kinetic study of FA reactions was conducted in 5 mL thick walled glass vials, consisting of 2 mL of 2-propanol solution of 1 wt % FA and 5-20 mM catalyst (CrCl_3 , YCl_3 or HCl). The reactor vials were heated to 90 °C, in a temperature controlled-aluminum block on a magnetic stir plate, and quenched in an ice bath at desired time points. The small glass reactors were used, instead of Parr reactor, because they require minimal heating time and to provide better data for the reaction kinetic model. This setup can only be used at low temperatures ($T \leq 120$ °C).

Product analysis

Products were identified with a gas chromatogram-mass spectrometer (GC-MS) system (Shimadzu QP 2010 Plus). Except for HMF, all quantifications were done in a GC (Agilent 7890 A), equipped with a HP-INNOWAX column, a flame ionization detector (FID) and a quantitative carbon detector (PolyarcTM). The PolyarcTM reactor converts organic compounds to methane and gives a universal response in the FID to eliminate cumbersome calibrations.³⁵ Product concentrations were determined using the calibration curve for FA and carbon numbers of the product molecules. The method was verified by the collapse of calibration curves for various organic compounds with different carbon numbers (Figure S1). HMF quantification was carried out with an Agilent 1200 Series high performance liquid chromatography (HPLC), equipped with a C-18 column (Agilent).

pH measurement

The pH of the solutions was measured with a glass pH electrode (Mettler Toledo InLab Science) and an Acumic basic AB 15 pH meter.

Spectroscopy techniques

Electrospray soft ionization mass spectra (ESI-MS) of the metal chloride solutions in 2-propanol were collected with a single quadrupole mass spectrometer (SQD2), using 2-propanol as mobile phase with the following parameters: capillary voltage 2.8 kV, extractor voltage 5 V, sample cone voltage, 20 V, source temperature, 363 K, desolvation temperature, 423 K, cone gas (N_2) flow, 40 L/h. X-ray absorption measurement (XAS) were performed at Cr K-edge ($Z = 24$, $E_0 = 5989\text{eV}$) in fluorescence mode, and Y K-edge ($Z = 39$, $E_0 = 17038\text{ eV}$) in transmission mode at Stanford Synchrotron Radiation Lightsource. Nuclear magnetic resonance ^1H NMR spectra of the post reaction solutions were recorded using a Bruker 400 MHz NMR spectrometer.

RESULTS AND DISCUSSION

Catalytic activity of metal chlorides for reductive etherification of HMF

Various metal chlorides (MCl_x) were screened for HMF reaction in 2-propanol and exhibited a wide range of catalytic activity under the same reaction conditions (Figure 1). While $ZnCl_2$ and $LaCl_3$ showed little activity, other salts gave more than 60% HMF conversion. In all the experiments, low HMF initial concentration of 1 wt % was used to minimize self-condensation of HMF to heavy products⁹ and enable focus on the mechanism of the main reaction. GCMS analysis revealed various products such as 5-(isopropoxymethyl)furfural **1** (mono-ether), 2,5-bis(hydroxymethyl)furan **2**, isopropyl levulinate **3**, 5-isopropoxymethylfurfuryl alcohol **4**, 2,5-bis(isopropoxymethyl)furan **5** (di-ether), 5-methyl furfural **6**, and 5-methyl furfural 2-(isopropoxymethyl) 5-methyl furan **7**. The observed products are similar to those of HMF reactions over Lewis acid zeolites (e.g., Sn-BEA) in alcohol solvents.⁸⁻⁹ We postulate a reaction network of HMF reaction in 2-propanol solution of MCl_x , consisting of three major pathways (Scheme 1). In pathway A, HMF etherification with 2-propanol forms **1**, which undergoes hydrolytic ring-opening to **3**. Pathway B proceeds via HMF transfer hydrogenation to **2**, followed by etherification to **4** and **5**. In pathway C, hydrogenolysis of HMF produces **6**, which is further reduced and etherified to **7**. Formation of hydrogenolysis products was also reported with solid Lewis acid Sn-BEA, presumably realized by in-situ H_2 generation and use.⁹ Further investigation of the hydrogenolysis pathway is outside the scope of this work.

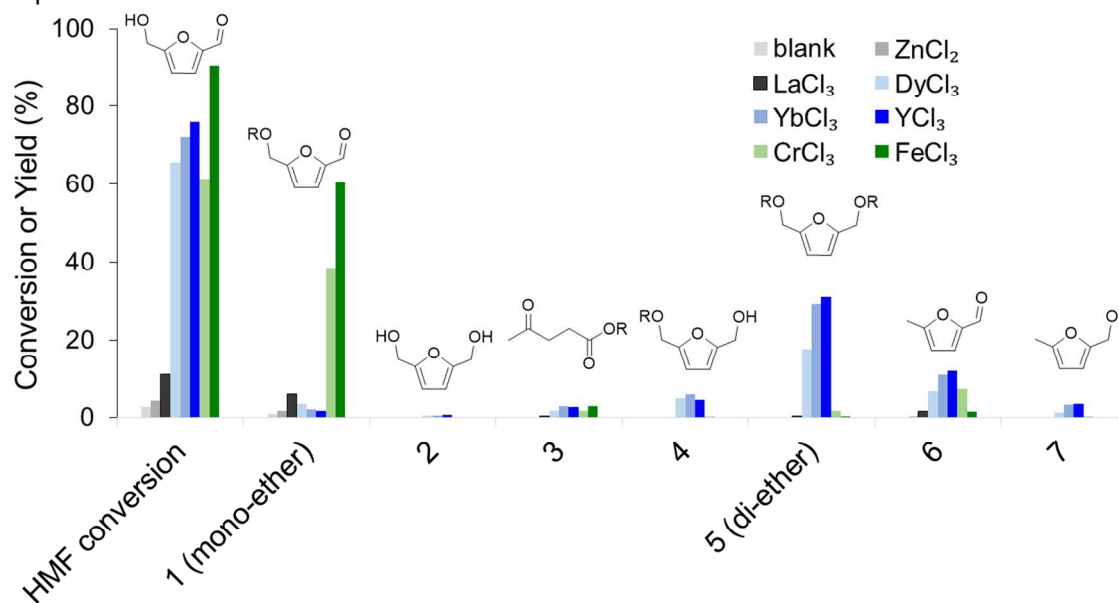
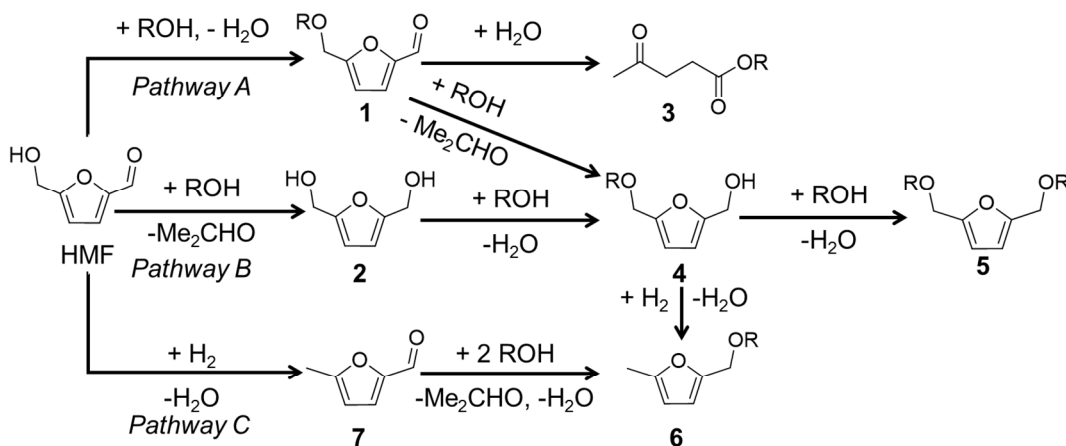


Figure 1: HMF conversion and product yields in 2-propanol catalyzed by variety of metal chlorides. Reaction conditions: 1 wt % HMF, 3 mM catalyst, 150 °C, 1 h reaction time. R represents an isopropyl group.

Among the tested catalysts, YCl_3 exhibited the highest activity for reductive etherification with approximately 35% yield to di-ether **5** without reaction-condition optimization. $DyCl_3$ and $YbCl_3$ also produced **5** as the major product at slightly lower yields. The post-reaction solutions turned dark brown due to significant polymerization. Nevertheless, our results demonstrate that some metal chlorides can

be potential catalysts for one-pot reductive etherification of HMF to the di-ether. Noticeably, the product distribution significantly depends on the metal. While YCl_3 , YbCl_3 and DyCl_3 favor reaction pathway B to the di-ether as stated, CrCl_3 and FeCl_3 selectively facilitate the direct etherification pathway A with up to 60% yield of the mono-ether **1**. The differences in activity and selectivity of MCl_3 for each pathway suggest the involvement of multiple catalytically active species and reaction mechanisms.

To untangle this complex reaction system, we used model compounds in order to study each reaction pathway independently: FA for direct etherification (pathway A); and furfural for reductive etherification (pathway B). CrCl_3 and YCl_3 were chosen as representative catalysts on account of their demonstrated chemoselectivity.

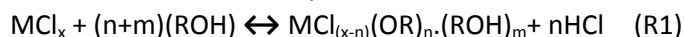


Scheme 1: Proposed reaction network of HMF reactions by MCl_3 in 2-propanol. OR = $\text{OCH}(\text{CH}_3)_2$

Furfuryl alcohol (FA) etherification

Reaction network

First, we investigate the direct etherification of FA. Mirroring the reactivity trend of HMF reaction (pathway A), CrCl_3 is significantly more active than YCl_3 , yielding 3.5 times as much ether (Figure S2). The low pH of the 10 mM MCl_3 solution (1.23 for CrCl_3 and 1.91 for YCl_3) indicates that the solutions are acidic, likely due to protons released from MCl_3 alcoholysis.

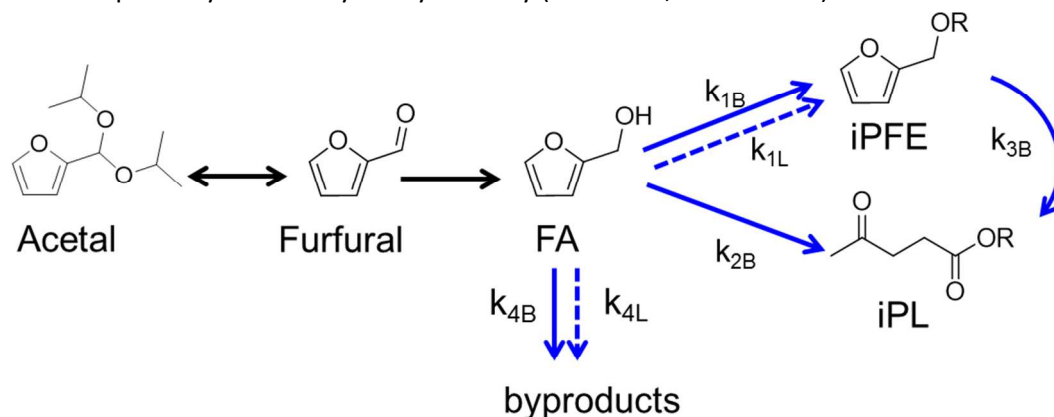


Multiple studies have attributed the activity of metal salts in FA reactions to their induced Brønsted acidity; the FA conversion and product yields qualitatively correlate with the solution pH.³⁶⁻³⁷ However, the pH measurement in alcohol solvent does not provide the true acid concentration because it largely depends on the solvent.³⁸ Our attempts to experimentally measure the induced HCl concentration by acid-base titration were unsuccessful, possibly due to the base interfering with the MCl_3 speciation. Moreover, measurements at room temperature to quantify the Hammett acidity do not reflect the true induced Brønsted acidity at elevated temperatures. Thus, a quantitative relationship between the reactivity of metal salts and the induced Brønsted acidity has yet to be established. In addition, the catalytic role of the Lewis acidic metal chloride species itself remains elusive.

To deconvolute the Lewis and induced Brønsted acid contributions of MCl_3 solutions, herein we develop a simple reaction kinetic model of FA reaction in 2-propanol starting with the product speciation. Aside from isopropyl furfuryl ether (iPFE), isopropyl levulinate (iPL) was identified as another major product, which is also a value-added chemical, reported to form via FA alcoholysis.^{11, 36-37, 39-41} Traces of 2-chloromethyl furan, α -angelica lactone, and dimerization products of furfuryl alcohol were

observed in GC/GCMS analysis. The post reaction solutions turned yellowish, probably due to FA polymerization. A typical time-dependent concentration profile shows that iPFE and iPL initially form in parallel, consistent with published work on FA alcoholysis in ethanol by Maldonado and co-workers.¹¹ The authors also suggested that the two minor pathways to ethyl levulinate are through ethyl furfuryl ether and 4,5,5-triethoxypentan-2-one (TEP) as intermediates. However, the corresponding 2-propanol analogue of TEP, 4,5,5-triisopropoxy-pentan-2-one (TIPP), was not observed in the course of our reactions. Interestingly, when ethanol or 1-propanol was used as the solvent, at the same reaction conditions, the corresponding trialkoxypentanones were detected as major products (Figure S3). The absence of TIPP suggests that the compound may not be stable in 2-propanol. As a result, we propose a FA reaction network, whereby iPL could form either directly from FA or via the iPFE intermediate (Scheme 2, blue arrows).

To assess to role of induced Brønsted acidity, experiments were performed with HCl in the absence of MCl_3 . Comparison of the selectivity for iPL and iPFE among CrCl_3 , YCl_3 , and HCl suggests that the FA reactions are not solely Brønsted acid catalyzed. The iPL to iPFE ratios for YCl_3 and CrCl_3 were higher than that for HCl, at the same FA conversion, indicating that FA etherification by MCl_3 was slightly more favored (Figure 2). Barbera et al. reported formation of furfuryl ether with either ZrO_2 (containing only Lewis acid sites) or sulfated ZrO_2 (containing both Lewis and Brønsted acid sites). Levulinate, on the other hand, was only observed in the presence of Brønsted acids (namely, after sulfation).⁴² These important findings have been incorporated into our reaction network, where now FA etherification and side reactions can be facilitated by either the Lewis acid, MCl_3 , or the induced Brønsted acid, HCl; while iPL formation pathways are catalyzed by HCl only (Scheme 2, blue arrows).



Scheme 2: Proposed reaction network of furfural reductive etherification in 2-propanol. Furfuryl alcohol reaction network in blue arrows

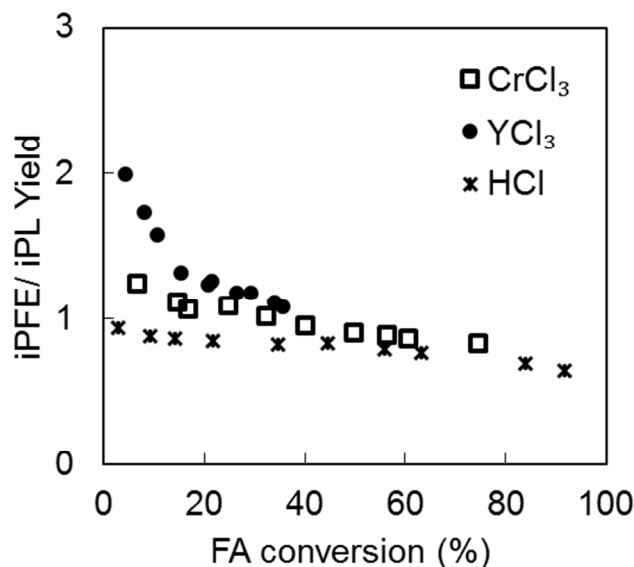


Figure 2: Selectivity to isopropyl furfuryl ether (iPFE) over isopropyl levulinate (iPL) in CrCl_3 , YCl_3 , and HCl . Reaction conditions: 1 wt % furfuryl alcohol, 90 °C, 10 mM catalyst.

Kinetic model

Using the proposed reaction network, we developed a simple kinetic model to assess the intrinsic catalytic activity of MCl_3 solutions. Due to the lack of *in situ* experimental methods to determine the acidity of MCl_3 solutions, the induced $[\text{HCl}]$ was assumed to be a linear function of $[\text{MCl}_3]$ within a rather small catalyst-concentration range (5-10 mM). (From the speciation equilibrium, one should expect a quadratic-like relationship between $[\text{HCl}]$ and $[\text{MCl}_3]$, which can be approximated as linear within a small range.) The assumed linearity is consistent with the linear correlation between $[\text{MCl}_3]$ and $[\text{HCl}]$ in aqueous solution predicted by the thermodynamic model OLI for various metal salts under similar reaction conditions (Figure S4; the OLI model has been validated in past work.^{21, 43}) The kinetic model assumes a perfectly mixed batch reactor and first-order dependence on the reactant and acid centers, as follows:

$$\frac{dC_{FA}}{dt} = -((k_{1B} + k_{2B} + k_{4B})[\text{HCl}] + (k_{1L} + k_{4L})[\text{MCl}_3])C_{FA}$$

$$\frac{dC_{iPFE}}{dt} = (k_{1B}[\text{HCl}] + k_{1L}[\text{MCl}_3])C_{FA} - k_{3B}[\text{HCl}]C_{iPFE}$$

$$\frac{dC_{iPL}}{dt} = k_{2B}[\text{HCl}]C_{FA} + k_{3B}[\text{HCl}]C_{iPFE}$$

$$\frac{dC_{byproducts}}{dt} = (k_{4B}[\text{HCl}] + k_{4L}[\text{MCl}_3])C_{FA}$$

$$\text{Induced acidity, } [\text{HCl}] = a[\text{MCl}_3] + b$$

where k_{iB} is the rate constant of the i^{th} Brønsted acid catalyzed reaction (solid arrows, black square, Scheme 2); k_{iL} is the rate constant of the i^{th} Lewis acid catalyzed reaction (dash arrows, black square, Scheme 2); and a and b describe the induced $[\text{HCl}]$. The model parameters were regressed to the experimental concentration profiles of FA, iPFE, iPL, and byproducts (determined by carbon balance) using the *lsqnonlin* nonlinear fitting function in Matlab. The regression procedure was similar to that used in our earlier work on the tandem isomerization/dehydration of glucose by CrCl_3 .⁴³ Specifically, the

model rate constants were fitted in two stages. First, we fitted the rate constants of the reactions catalyzed by HCl alone (Table 1). Then, we fitted the kinetic model for MCl_3 , including the parameters a and b (Table 1).

Representative transient profiles of FA and of the products show good agreement between the model and the experimental data (Figure 3). Comparison of the rate constants reveals that the Brønsted acid is substantially more effective for FA etherification than the Lewis acid metal species, with k_{1B} being 18-fold and 60-fold higher than k_{1L} for CrCl_3 and YCl_3 , respectively. A similar trend is observed for the side reactions. The superior reactivity of Brønsted acids for etherification has also been observed for solid acid catalysts. For example, Barbera *et al.* showed significant enhancement of ether formation after ZrO_2 sulfation.⁴² Recently, Schwartz and co-workers reported orders of magnitude higher rates for etherification by Brønsted acids (H-zeolites) than Lewis acids ($\gamma\text{-Al}_2\text{O}_3$).⁴⁴ Additionally, our model predicts that the concentration of induced HCl in CrCl_3 solution is nearly an order of magnitude higher than in YCl_3 solution (Figure S5). That is rationalized from the fact that Cr(III) is a stronger Lewis acid, making it easier for a solvated alcohol to lose a proton (alcoholysis) and produce a more acidic solution, similar to hydrolysis of the metal aqua cations.⁴⁵ Apparent rate constants ($k_{1\text{app}}$) were also determined to quantitate the overall observed reactivity (Figure 4). Clearly, *FA etherification by MCl_3 is primarily governed by the induced Brønsted acidity instead of the Lewis acidity*. Even though CrCl_3 is a more effective Lewis acid for etherification (higher k_{1L}) than YCl_3 , the substantially higher ether formation-rate observed for CrCl_3 is mostly attributed to the higher concentration of induced HCl.

Table 1: Predicted rate constants of furfuryl alcohol (FA) reactions in Scheme 2. Reaction conditions: 1 wt% FA, 90 °C, 5-10 mM MCl_3 , 5-20 mM HCl.

Brønsted acid catalyzed rate constant k_B ($\text{M}^{-1}\text{min}^{-1}$)				Lewis acid catalyzed rate constant k_L ($\text{M}^{-1}\text{min}^{-1}$)				Induced $[\text{HCl}] = a[\text{MCl}_3] + b$			
				CrCl_3		YCl_3		CrCl_3		YCl_3	
k_{1B}	k_{2B}	k_{3B}	k_{4B}	k_{1L}	k_{4L}	k_{1L}	k_{4L}	a	b	a	b
0.34	0.38	0.11	0.07	0.019	3.4e-3	5.6e-3	5.3e-4	0.235	8.1e-4	0.0264	1.7e-4

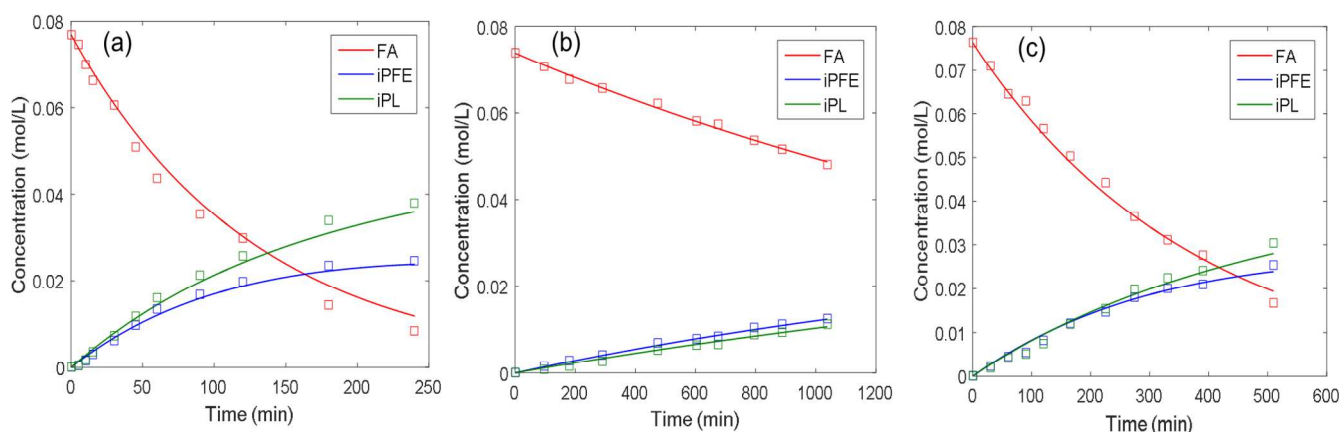


Figure 3: Experimental (symbols) and modeling (lines) concentration profiles of furfuryl alcohol (FA), isopropyl furfuryl ether (iPFE) and isopropyl levulinate (iPL) in HCl (a), YCl_3 (b) and CrCl_3 (c). Reaction conditions: 1 wt % FA, 10 mM catalyst, 90 °C.

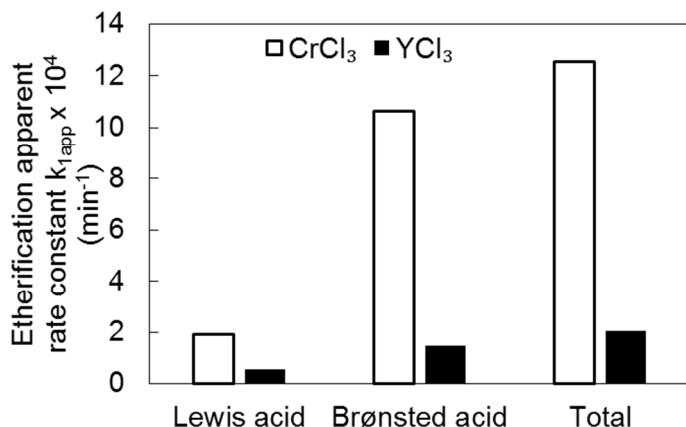


Figure 4: Apparent rate constant of furfuryl alcohol etherification $k_{1app} = k_1[\text{catalyst}]$ of 10 mM $CrCl_3$ and YCl_3 .

Furfural reduction

Reaction mechanism

Furfural was employed to study the reduction pathway B, Scheme 1. Isotopic tracing experiments in deuterated 2-propanol, in combination with GCMS analysis were carried out to investigate the furfural reduction mechanism by YCl_3 (Figure 5) and $CrCl_3$ (Figure S6). When 2-propanol solvent is unlabeled (2-propanol- d_0), the GCMS fragmentation of the FA product is the same as the FA standard, with the parent ion $m/z = 98$. However, in 2-propanol- d_8 ($(CD_3)_2CDOD$) solvent, the parent ion of the FA product is $m/z = 99$. A unit shift in the spectrum of FA produced in 2-propanol- d_8 indicates that one of the H atoms in the molecule has been replaced by a D, supportive of an intermolecular hydrogen transfer mechanism from 2-propanol to furfural. To examine the possibility of a dihydride mechanism, which usually occurs when catalysis involves a metal hydride,⁴⁶ 2-propanol-OD ($(CH_3)_2CHOD$) was used as the solvent. The GCMS closely resembles that in 2-propanol- d_0 , suggesting that there was no H scrambling between O of 2-propanol and α -C of furfural. Consequently, we inferred that both $CrCl_3$ and YCl_3 facilitate furfural reduction via an intermolecular hydrogen transfer (MPV) from α -C of 2-propanol to α -C of furfural.

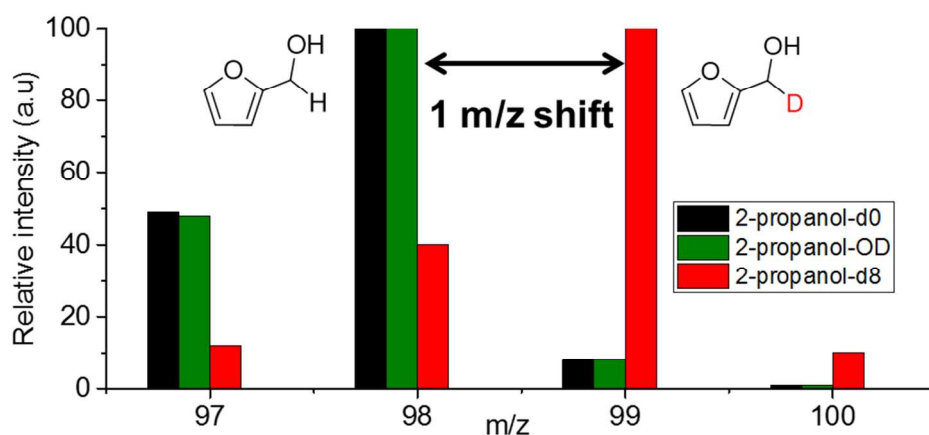


Figure 5: GCMS spectra of furfuryl alcohol product. Reaction conditions: 1 wt% furfural, 150 °C, 3 mM YCl_3 , in 2-propanol- d_0 ($t = 30$ min), 2-propanol-OD ($t = 30$ min), and 2-propanol- d_8 ($t = 1$ h).

1H NMR spectra of the post reaction mixtures in YCl_3 further support this conclusion by revealing the location of the replacing D (Figure 6). All three spectra in 2-propanol- d_0 , 2-propanol-OD and 2-propanol-

d8 display the four distinguished peaks of FA at around 7.4 ppm (H_a), 6.32 ppm (H_b), 6.27 ppm (H_c) and 4.54 ppm (H_d), where the first three peaks are assigned to the three H atoms on the furan ring, and the last peak belongs to H at α -C. The integrated peak ratio $H_d : H_c$ is equal to 2 : 1, corresponding to the relative number of H giving rise to the resonances, in standard FA, and FA product in 2-propanol- d_0 and 2-propanol-OD. However, in the 1H NMR spectrum in 2-propanol- d_8 , the $H_d : H_c$ peak ratio is 1:1, indicating that one of the H at the α -C was replaced by D. Primary kinetic isotope effect ($k_H/k_D = 2.22$) was observed when a 1: 1 by volume mixture of 2-propanol- d_0 and 2-propanol- d_8 was used as solvent, corresponding to $H_d : H_c$ ratio of 1.31. Attempts to carry out the same 1H NMR study for $CrCl_3$ were unsuccessful due to the paramagnetic nature of Cr, broadening the peaks and causing peak integration difficult. However, a mixture of unlabeled and labeled FA was observed in the GCMS of FA produced in 1:1 mixture of 2-propanol by $CrCl_3$, resembling that by YCl_3 and suggesting a similar kinetic isotope effect (Figure S7). Therefore, the intramolecular hydrogen transfer from α -C of 2-propanol to α -C of furfural is likely the rate determining step for furfural reduction by MCl_3 .

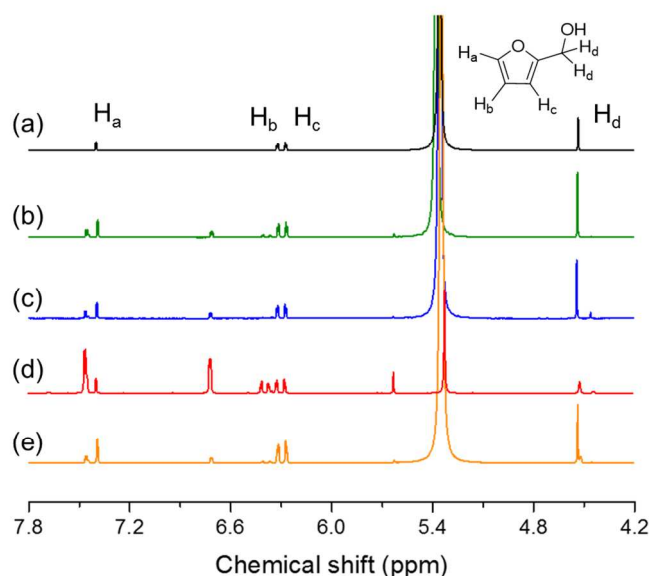


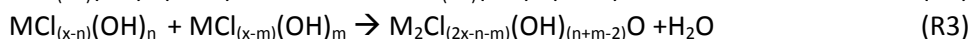
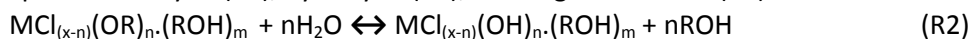
Figure 6: 1H NMR spectra of furfuryl alcohol standard (a) and post reaction mixture of furfural reduction by YCl_3 in 2-propanol- d_0 (b), 2-propanol-OD (c), 2-propanol- d_8 (d) and 1:1 mixture of 2-propanol- d_0 and 2-propanol- d_8 (e).

Determination of catalytically active species

Besides FA, identifiable products in GC/GCMS analysis include iPFE and iPL, as well as trace amounts of the aldol condensation product of furfural and acetone. Noticeably, 2-furaldehyde di-isopropyl acetal was detected instantaneously after furfural and the catalyst solution were mixed, and decreased over the course of the reaction. It suggests that acetalization of furfural and 2-propanol is a fast and reversible reaction, pointing to the overall reaction network in Scheme 2. Similarly to the observed activity trend for HMF, furfural reduction is considerably more favorable in YCl_3 , with nearly 10-fold higher FA yield than in $CrCl_3$ at the same reaction conditions (Figure S8). Given the lower Brønsted acidity of YCl_3 solutions compared with $CrCl_3$ solutions, the higher YCl_3 reactivity for furfural reduction indicates that the reaction is catalyzed by Lewis acid metal species.

Alcoholysis of a metal chloride in 2-propanol forms metal isopropoxide cations, which are highly sensitive to moisture and may be hydrolyzed in the presence of water⁴⁷⁻⁴⁸ in the $MCl_3 \cdot 6H_2O$ solution. The alcoholized/hydrolyzed metal ions may also condense to form metal clusters.⁴⁹ The various metal species have been detected in ESI-MS and XAS of MCl_3 solution in 2-propanol (see Figure S9 and Table S1

for more details). Consequently, MCl_3 speciation is hypothesized to proceed via the following generalized steps of alcoholysis (R1), hydrolysis (R2), and oligomerization (R3):



The various metal complexes possess different catalytic properties toward the reduction of furfural. Our previous studies on glucose isomerization by MCl_3 in aqueous solutions revealed $\text{M}(\text{OH})^{2+}$ as the active species.²¹⁻²² Adding excess HCl suppresses the hydrolyzed species, resulting in a drop of reactivity.²¹ In a similar vein, here we investigated how adding HCl to MCl_3 solutions would influence activity toward furfural reduction. In the case of YCl_3 , the furfural conversion and product yields drop monotonically with increasing $[\text{HCl}]$ (Figure 7a). Interestingly, the CrCl_3 activity exhibits a maximum at increasing HCl concentration before dropping (Figure 7b). HCl partly prevents alcoholysis/hydrolysis of MCl_3 (R1 and R2), i.e., the formation of partially hydrolyzed metal cations. Because CrCl_3 is much more likely to be alcoholized/hydrolyzed than YCl_3 , it is possible that hydrolyzed metal cations oligomerize (R3) due to their higher concentrations, thereby, reaching a maximum at an optimum $[\text{HCl}]$. Thus, we infer that the catalytically active species for furfural reduction are partially hydrolyzed metal cations. Computational studies of the mechanism of glucose isomerization by CrCl_3 have shown that the basic hydroxyl ligand on the metal center is essential, as it accepts a proton from the hydroxyl group at C2 carbon of glucose, which activates the intramolecular C2-C1 hydride shift at the Lewis acid metal center.²⁶ An analogous synergy might be drawn here for transfer hydrogenation of furfural. Overall, CrCl_3 and YCl_3 were shown to facilitate furfural reduction via the same intermolecular hydrogen transfer mechanism and have similar active species.

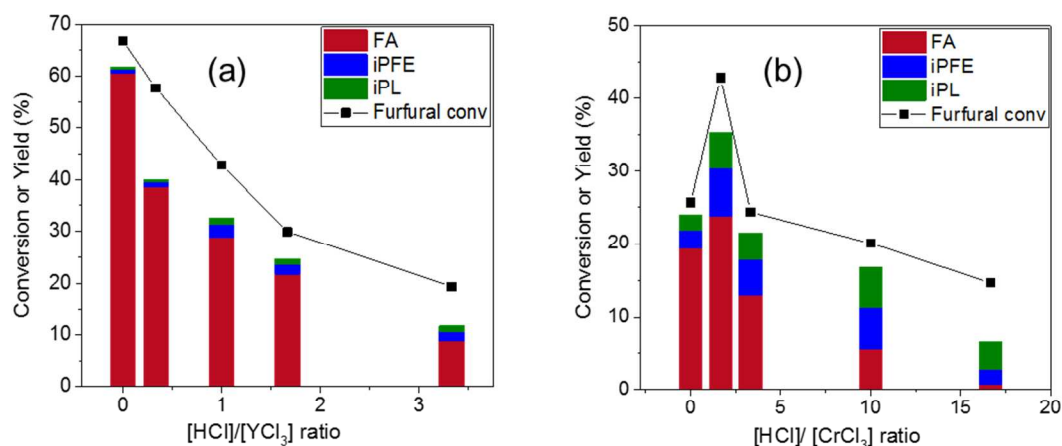


Figure 7: Effect of HCl addition on furfural conversion and product yields by YCl_3 (a) and CrCl_3 (b). Reaction conditions: 1 wt % furfural, 150 °C, 3 mM MCl_3 , $t = 30$ min (YCl_3), $t = 180$ min (CrCl_3).

Experiments with varying temperature were conducted to determine the activation energy for furfural reduction by MCl_3 . The rate constants were calculated using the initial-rate approach, specifically from the initial linear part of the time-dependent profile of the total amount of product formation (FA, iPFE, iPL). A lower apparent activation energy was found for CrCl_3 than for YCl_3 (25.6 vs. 30 kcal/mol) despite its lower rate (see Arrhenius plots in Figure S10). It should be noted that since the active species forms in-situ through metal salt alcoholysis/hydrolysis, its concentration is dependent on temperature. The higher apparent activation energy of YCl_3 could potentially be due to more hydrolyzed

metal cations formation at higher temperatures. The intrinsic reactivity of CrCl_3 and YCl_3 should only be compared at the same active species concentration, which is currently challenging to determine at reaction temperatures.

CONCLUSIONS

We have evaluated the catalytic activity of various metal chlorides for the tandem reductive etherification of HMF in 2-propanol. Two main parallel reaction pathways were identified: direct etherification to mono-ether, favored by CrCl_3 and FeCl_3 (pathway A), and reductive etherification to di-ether, preferred by YCl_3 , YbCl_3 and DyCl_3 (pathway B). To isolate each pathway, we employed model compounds: FA for pathway A and furfural for pathway B, with CrCl_3 and YCl_3 as representative catalysts. Through modeling of kinetic experiments, we quantified for the first time contributions from the Lewis acid metal species and from the induced Brønsted acidity, HCl, for FA etherification. The turnover frequency for etherification of FA by HCl is an order of magnitude higher than that by MCl_3 , suggesting that the etherification activity over metal chlorides is governed by the induced Brønsted acidity. CrCl_3 favors etherification over YCl_3 owing to its higher ability to alcoholize and produce protons. On the other hand, furfural reduction (hydrogenation) is facilitated by Lewis acidic species. We carried out isotopic labeling experiments to investigate the mechanism of furfural reduction. GCMS and ^1H NMR analysis revealed that intermolecular hydrogen transfer from the α -C of 2-propanol to the α -C of furfural is the rate-determining step. Based on the correlation between the effect of HCl addition on the speciation of metal salts and on the MCl_3 activity for furfural reduction, we hypothesized that the catalytic active species for the transfer hydrogenation is a partially hydrolyzed metal cation, similar to the active species in glucose isomerization by MCl_3 in aqueous solution. The mechanistic understanding and methodology introduced in this work could provide insights into Lewis and Brønsted acid catalysis in organic media for other reactions.

ASSOCIATED CONTENT

Supporting Information:

The supporting Information available: additional experimental details, figures, tables, and references. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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DISCLAIMS

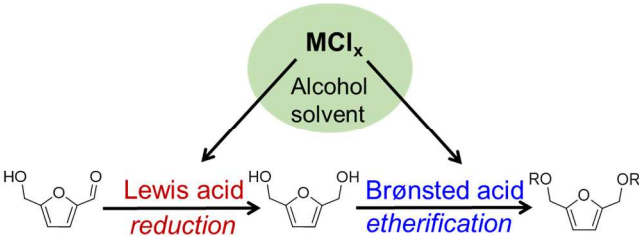
The authors declare no competing financial interest.

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Graphical Abstract



Role of Lewis and Brønsted acid of metal chloride catalysis in reductive etherification of HMF