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Activation of Carbonyl-Containing Molecules with Solid Lewis Acids in Aqueous Media

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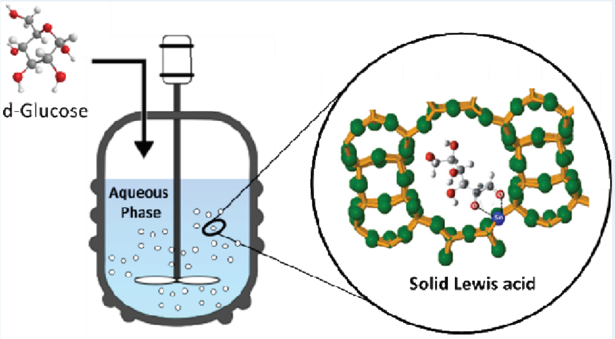
ABSTRACT: Current interest in reacting carbonyl-containing molecules in aqueous media is primarily due to the growing emphasis on conversion of biomass to fuels and chemicals. Recently, solid Lewis acids have been shown to perform catalytic reactions with carbonyl-containing molecules such as sugars in aqueous media. Here, catalysis mediated by Lewis acids is briefly discussed, Lewis acid solids that perform catalysis in aqueous media are then described, and the review is concluded with a few comments on the outlook for the future.

KEYWORDS: Lewis acid, biomass, water-resistant catalysts



INTRODUCTION AND SCOPE

Reactions of carbonyl groups that are activated by Lewis acids are involved in several important organic and biochemical transformations.[1,2] Coordination of the carbonyl oxygen to a Lewis acid site induces polarization in the molecule, effectively enhancing its reactivity by augmenting its electrophilicity. The most common solvents used for Lewis-acid-catalyzed reactions are aprotic and nonpolar, since protic polar solvents suppress Lewis acidity by hindering coordination or irreversibly decomposing the catalyst. Despite the disadvantages of protic polar solvents, the field of Lewis acid catalysis in water has been receiving increased attention in recent years. One reason for this interest is an environmentally driven shift toward using nontoxic solvents for organic reactions.[3,4] However, the major driving force for recent work on Lewis acids in water is the conversion of biomass to fuels and chemicals.

The growing interest in carbonyl chemistry fueled by recent efforts to use biomass as a sustainable source of carbon to supply compounds needed in the transportation and chemical sectors has provided motivations to develop Lewis-acid catalyzed reactions in aqueous media.[5−10] Most thermochemical routes for biomass conversion involve molecules containing carbonyl functionality. For instance, cellulose acid hydrolysis primarily produces aldoses and ketoses; bio-oil obtained from fast pyrolysis contains a range of carboxylic acids, aldehydes, and ketones; and acid-catalyzed dehydrations of monosaccharides produce furfural-based heterocycles. Downstream conversions of these oxygenates require the use of catalysts that can selectively activate their carbonyl groups to promote desired reaction pathways, such as C−C-bond-forming condensations and isomerization reactions. However, high oxygen content causes these molecules to have low thermal stability and high boiling points. These properties and others necessitate processing at low temperatures and in condensed (generally aqueous) phases, and most catalysts are not optimized to work under these conditions.[11] It is not surprising that the development of hydrothermally stable and active catalysts is one of the major bottlenecks in the transition to a biomass-based economy.[12] Thus, the discovery of new catalytic materials capable of controlling the reactivity of carbonyl-containing molecules to efficiently depolymerize, deoxygenate, and upgrade biomass in the presence of water is a topic of current relevance.

We envision that heterogeneous catalysts that promote Lewis acid chemistry in aqueous media will provide exciting opportunities to manipulate and control the construction of diverse molecular building blocks from biomass. Here, we focus our review on the use of Lewis acids to activate carbonyl-containing molecules in the presence of water. Comprehensive literature coverage of all organic transformations catalyzed by Lewis acids is not provided. Rather, recent work on the transformations of biomass-derived molecules using solid Lewis acids in aqueous media is presented, giving special attention to the use of isolated Lewis acid sites embedded in microporous and mesoporous silica matrices. The review is divided into two main sections. The first section presents a general introduction to Lewis acid chemistry. An emphasis is placed on complex formation between Lewis acids and carbonyl groups and the influence of water on Lewis acid−Lewis base interactions. The second section presents recent work on reactions catalyzed by Lewis acids involving biomass-derived carbohydrates in aqueous media. With the examples discussed in this work, we hope to highlight important

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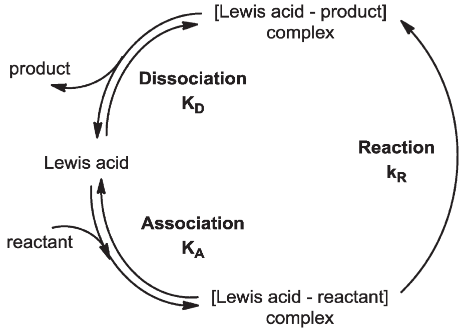


Figure 1. Schematic representation of a typical catalytic cycle involving a Lewis acid catalyst.

Table 1. Classification of Cations According to HSAB Theory[a]

hard	borderline	soft
H^+	Ni^{2+}	Cu^+
Ti^{4+}	Fe^{2+}	Cd^{2+}
Al^{3+}	Cu^{2+}	Hg^{2+}
La^{3+}	Zn^{2+}	Au^+
Sn^{4+}	Co^{2+}	Ag^+

[a] From ref 16.

factors influencing carbonyl activation using solid Lewis acids in water while also providing insights for potential future research directions in the area of biomass conversion.

■ OVERVIEW OF LEWIS ACID CHEMISTRY IN WATER

1.1. Lewis Acid Theory. The acid–base theory developed by Lewis revolves around the central concept of adduct formation and dissociation through electron pair sharing.[13] A Lewis acid is defined as a molecule that can accept a pair of electrons, while a Lewis base is an electron pair donor. A typical catalytic cycle mediated by a Lewis acid is depicted in Figure 1. First, an adduct is formed by coordination of the Lewis acid with a Lewis base. Typical Lewis basic sites consist of one or more oxygen or nitrogen atoms within a molecule. Next, the Lewis basic site is activated (i.e., it becomes more prone to undergo chemical transformation) by transferring electron density to the acid in a manner proportional to the energy difference and degree of overlap between the occupied orbitals of the base and the empty orbitals of the acid. The resulting polarization increases the electrophilicity of the molecule, making it more susceptible to nucleophilic attack. After the chemical transformation has proceeded, the Lewis acid-product complex dissociates, making the catalyst available for another catalytic cycle. Overall reaction rates are determined by the relative proportion of rate constants for the association (K_A), reaction (k_R), and dissociation (K_D) steps. Kinetic studies have shown that efficient Lewis acid complexation with the Lewis basic site (i.e., high K_A values) is needed to obtain appreciable overall reaction rates; in general, good coordination is associated with efficient catalysis as long as product inhibition is not excessive.[14]

The Lewis theory is quite broad and can be used to explain most acid–base processes. For instance, the Brønsted–Lowry acid theory, which defines an acid as a molecule capable of giving protons, is indeed a special case of the Lewis acid theory whereby a proton acts as an electron acceptor and proton transfer is the net result of two Lewis processes involving adduct dissociation and adduct formation. Thus, quantification of Lewis acid strength is quite challenging because it applies to a wide range of species that undergo multiple interactions. Several approaches have been proposed to define Lewis acid character. Lewis acidity of cations has been directly related to their charge and inversely related to their size.[15] Cations with more positive charges have a greater tendency to accept electron pairs from Lewis bases, while at the same charge level, smaller cations can more readily accept electrons than larger ones.

The hard–soft acid–base (HSAB) theory is a more accepted approach that does not rely on electronegativity or other macroscopic properties.[16] Instead, Lewis acids and Lewis bases are divided into hard and soft groups, in which hard species are small, not very polarizable molecules with highly localized charges, and soft species are large, polarizable molecules with highly delocalized charges (see Table 1 for a list of hard and soft Lewis acids). The theory predicts high stability and reactivity values only for hard-acid/hard-base and soft-acid/soft-base complexes.[16–19] Unfortunately, the predictive value of the HSAB theory is limited to a narrow range of Lewis bases and, therefore, can be used only in a qualitative sense. More complex approaches based on numerical and quantum chemical calculations have been developed,[20,21] yet quantitative prediction of Lewis acid–Lewis base complex stability and full understanding of the complex interactions with solvent molecules has not been accomplished.

In contrast to the vast amount of studies that exist to quantify the hard–soft character of homogeneous Lewis acids, significantly fewer approaches have been reported for the characterization of solid Lewis acids. This is partly due to the fact that solid acids possess a distribution of sites with fluctuating degrees of both Brønsted and Lewis acidity. In this regard, a common practice is to use test reactions that probe for a specific type of acidity in conjunction with thermoanalytical, spectroscopic, resonance, and chemical methods to characterize the nature of acid sites. Significant literature exists that summarizes these methodologies in more detail, and therefore, this topic will not be discussed further in this review.[2,22–25]

1.2. Lewis Acid-Lewis Base Interactions. *Carbonyl Complex Formation.* Multiple modes of coordination can occur between Lewis acids and carbonyl groups, each with a different impact on reactivity.[26] Figure 2 depicts the most common coordination schemes; they are described as follows:

(A) *Electrostatic interaction* is the simplest coordination mode; it involves a Lewis acid center situated at the negative end of the C=O dipole generating a C–O-(Lewis acid) complex with a bond angle of 180°.

(B) *σ Bonding* occurs when carbonyl groups interact with Lewis acids through one of the oxygen atom lone pairs with the metal being in the nodal plane of the C=O π bond. This coordination mode is the most common among main-group Lewis acids.

(C) *π System coordination* is observed when interactions occur through the π orbital system by way of η^2 coordination of the metal to form a metalloxirane complex. In this mode, the carbonyl π orbital acts as the donor, but with back-bonding into the C=O π^* orbital also occurring. This mode of coordination is more common with transition metals.[27,28]

(D) *Double coordination* of carbonyl compounds by two Lewis acid sites is theoretically possible, but coordination of

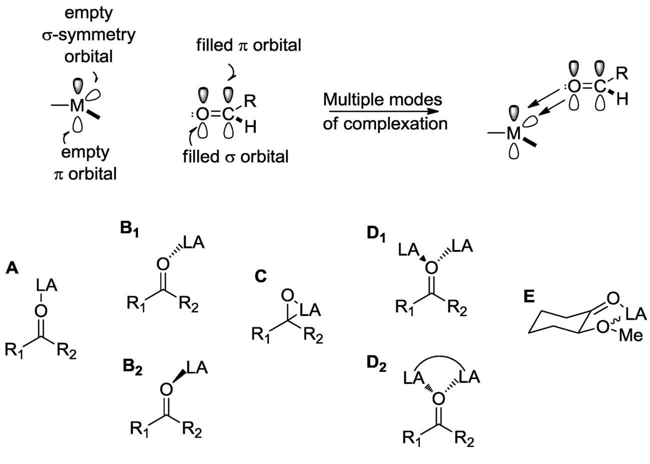


Figure 2. Modes of complexation between Lewis acids (LA) and carbonyl groups. (A) Electrostatic interaction, (B) σ-bonding, (C) coordination through π systems, (D) double coordination, (E) chelation.

two individual Lewis acids (D1) has not been observed due to the high preference for single coordination modes, even in the presence of excess Lewis acids. Nonetheless, double coordination by bidentate Lewis acids (D2) has been observed experimentally, and it has been related to significant enhancements in reactivity.[29,30]

(E) *Chelation* occurs when Lewis acids coordinate with molecules bearing a Lewis basic heteroatom in close proximity to the carbonyl moiety (e.g., in the α, β, or γ position). This type of coordination can bring an enhancement on reactivity by withdrawing electron density from the molecule while also leaving only one plane available for reaction. Thus, chelation control with Lewis acids is an important tool to guide product stereoselectivity.[31−34]

Understanding the coordination modes of carbonyl−Lewis acid complexes is important when considering the various factors influencing Lewis acid reactivity. Several theoretical and experimental studies have been performed to predict and identify the impact of complex conformation for a number of Lewis acid-catalyzed reactions. For example, the influence on frontier molecular orbitals of acrolein−Lewis acid complexes during Diels−Alder reactions was studied with quantum chemical and ab initio methods.[35] It was observed that acrolein-derived Lewis acid complexes have lower LUMO energy levels and exist mostly in the s-trans conformation, in contrast to uncomplexed α,β-unsaturated carbonyl compounds. NMR studies have been used to identify complexes in several organic reactions, including Mukaiyama aldol reactions, the allylstannane addition to aldehydes, and the addition of allylsilanes to aldehydes and α,β-unsaturated ketones.[36−39] It was determined that mostly σ-bonded complexes dominate the reaction chemistry. However, interesting studies involving bidentate molecules capable of coordinating one carbonyl group to two Lewis acid centers simultaneously have shown substantial reactivity enhancements in Mukaiyama aldol reactions, Michael additions, and Meerwein−Ponndorf−Verley (MPV) reductions of aldehydes when compared with their monodentate σ-bonded counterparts. The bidentate Lewis acids enhanced the reactivity of carbonyl toward hydride transfer via the double electrophilic activation of the C═O moiety.[40−44] For instance, as seen in Table 2, aluminum isopropoxide is not capable of catalyzing the MPV reduction of benzaldehyde using 2-propanol at room temperature, whereas a molecule featuring two aluminum isopropoxide moieties in close proximity achieves full conversion at room temperature almost instantaneously.[40] Given the reduced association equilibrium constants for carbonyl groups with Lewis acids found in aqueous systems, it appears that the activation of carbonyl groups using bidentate molecules may hold promise in improving reactivity.

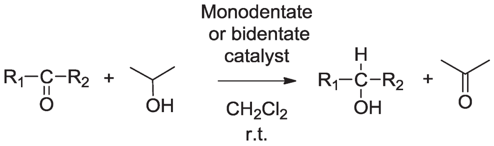
1.3. Lewis Acid−Solvent Interactions: Effects of Water.

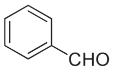
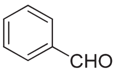
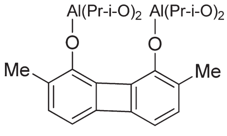
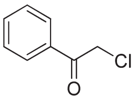
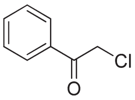
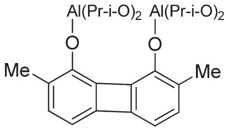
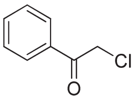
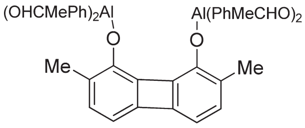
The interaction of solvent molecules with Lewis acids drastically influences catalytic activity. Unfortunately, the presence of water usually has a detrimental effect on Lewis acid reactivity. Specifically, solvents that exhibit a Lewis base character will compete with Lewis bases to coordinate with open acid sites. Like the HSAB theory, several predictors exist to assess the Lewis basicity of solvents. The Gutmann's donor number (DN) is based on the enthalpy change for the coordination of an isolated solvent molecule to a hard Lewis acid ($SbCl_5$) in dichloroethane.[45] It provides a qualitative sense of the relative interaction of polar and nonpolar solvents with Lewis acids. The low DN values typically observed for aprotic nonpolar solvents suggest that they coordinate weakly to hard acid sites, whereas the high values seen for polar solvents suggest that very strong interactions with Lewis acids occur (see Table 3). Water has a DN value of 18, in contrast to benzene's DN value of 0.1, thus suggesting that strong water−Lewis acid interactions need to be disrupted for successful coordination between the Lewis acid and the Lewis base site. Consequently, catalysis by Lewis acids in water should be less effective when compared with other solvents.

Solvents with hydrogen bond donor capacity can also behave as Lewis acids by interacting with Lewis basic sites. The electron pair acceptor capacity (AN) and the hydrogen bond donor acidity (α) are parameters commonly used to assess Lewis acid character in solvents.[45−47] Table 3 lists values for several common solvents. Water, having high AN and α values, has a strong tendency to accept electrons from Lewis bases. Therefore, the efficiency of Lewis acid catalysis will be further inhibited by the presence of water. Metal salts (e.g., $AlCl_3$, $TiCl_4$, BF_3) are the most common type of Lewis acid catalysts. Their Lewis acid character emerges from the ability of their cations to attract electron pairs. Upon dissolution in water, cations quickly complex with water molecules, forming aqua ions. For cations with oxidation states of 1, 2, or 3, the chemical formula for these ions is $[M(H_2O)_n]^{z+}$, where n (the solvation number) typically ranges between 4 and 6.

For higher oxidations states, hydroxo and oxy anions will also be present. The strength of the bonds between the metal ion and water molecules in the primary solvation shell increases with the electrical charge (z) of the metal ion and decreases with its radius (r).[15] Thus, coordination of a Lewis base to a cationic Lewis acid in water will depend on the ability of the ligands to replace the coordinated water molecules. Aqua ions of typical hard Lewis acids have diminished Lewis acid character, although it has been reported that $Al(H_2O)_6^{3+}$ (i.e., the aqua ion of $AlCl_3$) is active in the aqueous phase azidolysis of α,β-epoxycarboxylic acids.[48] Once formed, aqua ions will invariably undergo hydrolysis reactions to produce hydroxide or oxide species, consequently losing most of their Lewis acid character. Cations most resistant to hydrolysis for their size and charge are hard pretransition metal ions or lanthanide ions, followed by transition metal ions and soft ions of post-transition metals. The ions that show the strongest tendency to hydrolyze for their charge and size are Pd^{2+}, Sn^{2+}, and Hg^{2+}.[49,50] Due to this irreversible decomposition, most Lewis acid chemistry is usually performed under strict anhydrous conditions.

Table 2. MPV Reaction Using Monodentate and Bidentate Al Complexes[a]



Entry	Substrate	Al reagent	Hydride source	Conditions	Yield [%]
1		Al(Pr-i-O)₃ (1 eq)	*i*-PrOH (1 eq)	r.t., 2 h	10
2		 (1 eq)	*i*-PrOH (1 eq)	r.t., 1 min	>99
3		Al(Pr-i-O)₃ (1 eq)	*i*-PrOH (1 eq)	r.t., 2 h	N.R.
4		 (5 mol%)	*i*-PrOH (1 eq)	r.t., 2 h	75
5		 (5 mol%)	PhMeCHOH (1 eq)	r.t., 2 h	>99

[a] From ref 40.

Thermodynamic analyses of Lewis acid complexes show that association equilibrium constants for the coordination of hard monodentate reactants to Lewis acid sites in water are generally small, ranging from 10^{-2} to 10^{0} M^{-1}.[51−55] More favorable equilibrium constants are achieved through chelation or bidentate coordination when two basic sites within the same molecule bind to a Lewis acid center containing two open coordination sites. Increased stability of the complex is associated with a gain in entropy upon release of solvent molecules into the bulk phase when coordination of the second Lewis base occurs. Studies on Diels−Alder reactions have shown that equilibrium constants for bidentate coordination of reactants in water are typically 2−3 orders of magnitude larger than those observed for monodentate binding.[56,57] For this reason, it is expected that mostly bidentate-type interactions will be encountered in Lewis acid catalysis in water.

1.4. Water-Tolerant Lewis Acids. *Water-Soluble Salts.* Lanthanide-based salts have been reported to act as hard Lewis acids in the presence of water without undergoing severe hydrolysis.[58−62] Specifically, lanthanide triflate salts were shown to be highly active catalysts for the aldol reaction of silyl enol ethers with aldehydes using commercial aqueous formaldehyde solutions in THF.[3] Lanthanide compounds are known to have strong affinities toward carbonyl oxygens as a result of their hard Lewis acid character. In the particular case of triflate salts, Lewis acidity is enhanced by the added electron-withdrawing effect of the trifluoromethanesulfonyl anion. Importantly, on the basis of their hydrolysis constants and hydration energies, most lanthanide triflates exhibit very slow hydrolysis rates.[63]

Table 3. Gutmann's Donor Number (DN), Acceptor Number (AN), and Hydrogen Donor Acidity (α) Parameter Values for Common Solvents[a]

solvent	DN	AN	α
benzene	0.1	8.2	−0.3
acetonitrile	14.1	19.3	0.19
methanol	19	41.3	0.93
dimethylsulfoxide	29.8	19.3	0
water	18	54.8	1.17

[a] From refs 45−47.

The hydration enthalpies of the trivalent lanthanide ions show increasingly negative values as the atomic number increases, in line with the decrease in ionic radius known as the lanthanide contraction. Hydrolysis constants (K_h) and water exchange rate constants (WERC, defined as the exchange rate constant for substitution of inner-sphere water ligands), have been directly related to catalytic activity in aldol reactions.[63] It was found that reaction systems using cations with pK_h and WERC values higher than 4.3 and 3.2×10^6 M^{-1} s^{-1}, respectively, always generated product yields greater than 50%, regardless the type of anion used. For active cations, using triflate or perchlorate instead of chloride anions resulted in improved yields and longer catalytic lifetimes.[63] The use of amino acid cocatalysts in conjunction with Lewis acid salts has been recently shown to improve activity and stereoselectivity in asymmetric aldol reactions performed in mixed aqueous/organic solvent systems.[64] A possible explanation for these results involves a concerted effect wherein on one hand, there is an L-proline-mediated activation of the ketone via an enamine intermediate and, on the other, an L-proline complexation with metal salts to form an adduct responsible of activating the aldehyde partner.[64]

Metal Oxides. Metal oxides are known to show both Lewis and Brønsted acidity in the presence of water, for example: The relative population and strength of both types of sites depend on the type of metal as well as pretreatment and reaction conditions. Metal oxides are usually crystalline solids that exhibit a nearly ionic bond between the oxygen and metal atoms. Consequently, at the surface, corners, and edges of exposed crystal planes, coordination of ions is incomplete with respect to the coordination in the bulk, giving rise to Lewis acid sites (located in the coordinatively unsaturated cations) and Lewis basic sites (located in the oxide anions). In the presence of water, surface hydroxyl groups with Brønsted acidity are generated. For example, alumina exhibits increased Lewis acidity when it is calcined at temperatures above 450 °C due to the generation of anionic vacancies formed by three or more Al^{3+} cations located in close proximity.[65] The combination of two metal species can generate binary oxide mixtures with enhanced acidity.[66−68] Improved Lewis acid strength in these mixtures has been correlated to excess positive charge in the crystal, and as a result, qualitative relations have been developed using the averaged electronegativity of cations.[69,70]

The influence of water on the acidic properties of these oxides and oxide mixtures continues to be a heavily studied topic. Water molecules are prone to undergo dissociation processes on metal cations as a function of the cation's electronegativity.[71] In solids, Lewis acids can interact with water molecules and reversibly interconvert into sites with varying degrees of Brønsted acidity by dissociating protons from a water molecule. Several studies have reported on drastic reaction rate increases during acid-catalyzed reactions (e.g., hydrolysis, esterification, dehydration, and isomerization) upon exposing metal oxides to water. Specifically, for 2-butanol dehydration reactions using MoO_3/ZrO_2 catalysts, a 5-fold increase in conversion was observed when at least 20% water was cofed in the gas stream, followed by a decrease in activity upon cessation of water vapor flow.[72] It was suggested that Brønsted acid site generation resulted from the following reaction occurring at the metal centers on the surface of the support:

$$MoO_x - Zr + H_2O \rightleftharpoons MoO_x(H_2O) - Zr \rightleftharpoons MoO_x(OH)^- - Zr + H^+$$

Similar effects were observed for 2-butanol dehydration rates using Nb-based catalysts in the presence of water vapor,[73] for hydrolysis of triglycerides using tungstated zirconia (WZ) catalysts,[74] and during esterification of acetic acid using modified zirconias.[75] In all cases, spectroscopic and thermoanalytical data showed a sharp, yet reversible, increase in the number and strength of Brønsted acid sites upon exposure to water. Detailed kinetic investigations on support effects on alcohol dehydration rates using supported tungsten oxide domains indicated the formation temporary acidic $H^{\delta+}(WO_3)_n{}^{\delta-}$ species upon reduction of surface WO_x precursors by alcohol moieties.[76] However, further investigations are needed to fully understand the impact of water molecules on acidity, given that water molecules can create a strong hydration shell around Brønsted acid sites, thereby effectively decreasing their strength,[77] and also given that water may not always convert Lewis acid sites into Brønsted acid sites.[78]

Metalloid (i.e., elements that are near the metal−nonmetal dividing line in the periodic table, including B, Si, Ge, and As) oxides can be either crystalline or amorphous and generally feature covalent bonding between the oxygen and metalloid atoms. Their surface atoms feature coordinatively unsaturated sites; however, these sites are very reactive and irreversibly form surface hydroxyl groups upon contacting water. These hydroxyl species feature weak Brønsted acidity and virtually no Lewis acidity. The incorporation of an element of a lower valency state into the matrix (e.g., the incorporation of alumina into amorphous silica or into crystalline silicalite) generates a negative charge in the structure. When a proton is used to balance the charge, a strong Brønsted acid site is generated. If, however, the lower valence element is removed from the framework, the charge imbalance disappears and Lewis acidity reappears, as the material increasingly resembles a metal oxide supported on a metalloid matrix. A classic example of this phenomenon is the appearance of extra-framework aluminum (EFAl) after aluminosilicate zeolites are subjected to a steaming process at elevated temperatures. Although the impact on catalytic activity of Brønsted and Lewis acid sites within metal/metalloid oxides has been reported for several reactions in the absence of water,[79−82] the exact nature of active sites in the presence of water remains controversial. Regardless, as it will be shown below, Lewis acid sites in metal oxides can play an important role in catalyzing reactions in the aqueous phase.

Microporous and Mesoporous Solids Containing Isolated Lewis Acid Sites. Zeolites can have both Brønsted and Lewis acid sites that originate from the aluminum atoms that reside in the framework. These Lewis acid sites in zeolites that also contain Brønsted acid site have been investigated for quite some time. Thus, we will not review that literature here. However, beginning with the discovery of titanium silicalite-1 (TS-1) in the early 1980s, isolated Lewis acid sites in crystalline microporous materials could be obtained with the absence of Brønsted acid sites.[83] TS-1 is a crystalline, microporous material with the ZSM-5 framework topology. The framework is primarily silicon dioxide (pure silicon dioxide would be called silicalite-1) with a few weight percent of the silicon substituted by Ti^{4+}. Surprisingly, when the Ti substitutes for Si, it remains tetrahedrally coordinated and thus does not create any Brønsted acid sites; however, the framework Ti does create an isolated Lewis acid site. In addition, since the framework is primarily crystalline silicon dioxide, the overall structure is somewhat hydrophobic. TS-1 is active in many organic transformations, and, importantly, is able to maintain activity even in the presence of a bulk water phase.[84] TS-1, in combination with aqueous solutions of hydrogen peroxide (H_2O_2), has provided for the industrial implementation of various reactions, including phenol hydroxylation, cyclohexanone ammoxidation, and propene oxide synthesis, with great simplification of the processes and reduction of waste and hazards.[84−87]

The remarkable performance of TS-1 is attributed to the presence of isolated tetrahedral Ti^{4+} atoms in framework

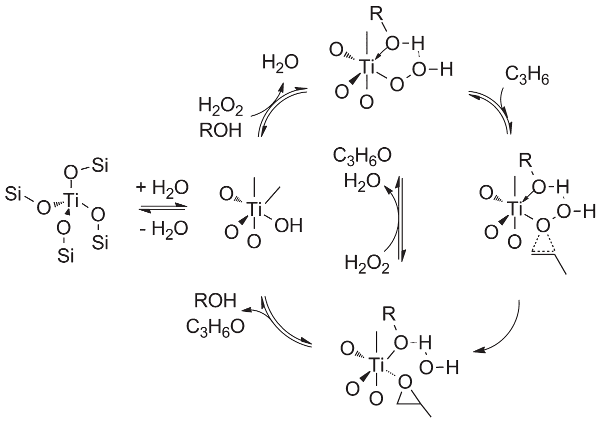


Figure 3. Proposed reaction mechanism for an epoxidation reaction using TS-1. From refs 88 and 90.

positions that are located in a hydrophobic environment. The tetrahedrally coordinated Ti^{4+} center can act as a Lewis acid by using empty d^0 orbitals to accept electron pairs from reactants. Figure 3 shows a proposed mechanism for a TS-1-mediated epoxidation that illustrates the activation of hydrogen peroxide in the presence of water. The first step involves the adsorption of a molecule of H_2O_2 to form a Ti–OOH species that is hydrogen-bonded with an alcohol or water molecule. In the epoxidation step, the attack on the double bond by the peroxy oxygen vicinal to Ti leads to the formation of the epoxide, a Ti-alkoxide, and a water molecule. The final step involves desorption of the epoxide and reaction of the Ti-alkoxide with water to form the original Ti site .[88−90] Although the precise epoxidation mechanism is still under debate, a general consensus exists that TS-1 coordinates H_2O_2 to form a Ti–OOH species, which plays a central role in the catalytic cycle.[91,92] To accommodate larger substrates, Ti^{4+} has also been introduced into the framework of 12-membered ring zeolites (Ti–Beta) and into ordered mesoporous silica matrices (Ti-MCM41).[93] Larger substrates were able to be processed in these solids with larger pores; however, in some cases, lower reactivity with respect to TS-1 was observed, suggesting that the location of Ti sites and the environment surrounding the site influence activity.[94−96]

The successful catalytic results obtained with Ti-containing zeolites paved the way for the synthesis of new zeolites and mesoporous materials containing different metals in framework positions. Tin (Sn), zirconium (Zr), tantalum (Ta), and niobium (Nb) have been successfully incorporated into the framework of zeolite Beta and MCM-41, each exhibiting peculiar catalytic properties different from Ti-based zeolites in the presence of water.[97−106] For example, Sn and Zr Beta are also active catalysts for oxidations with H_2O_2; however, unlike Ti zeolites, they are inactive in epoxidation reactions. Instead, both solids are capable of performing Baeyer–Villiger oxidation reactions whereby a ketone is transformed into a lactone.[106−110] Sn, Zr, Ta, and Nb Beta zeolites are active in the MPV reduction of aldehydes to ketones and in the etherification of alcohols.[99,105,111,112] Importantly, in the course of these investigations, neither the Baeyer–Villiger nor the MPV reaction was performed in 100% aqueous media, and although it was observed that the catalytic activity did decrease in the presence of small amounts of water,[99] these materials nonetheless had some remaining activity (in sharp contrast to their homogeneous chloride-salt counterparts).

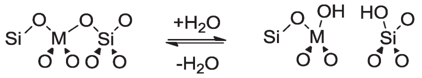


Figure 4. Two possible types of sites, a closed (left) and an open (right) site, for a metal center in the framework of a zeolite.

Recently, it was shown that zeolites with the Beta topology that contain tin (Sn–Beta) or titanium (Ti–Beta) are highly active catalysts for the isomerization of glucose to fructose in 100% aqueous media and that the reaction mechanism was truly a Lewis-acid-mediated conversion.[113,114] This is the first example of proven Lewis acid catalysis in pure water using a zeolite-based catalysts (more discussion of this work is provided below). Althoguh there has been significant published work on the characteristics of the titanium center in TS-1, all solids discussed here that contain isolated Lewis acid sites (including TS-1) require much further investigation from both theoretical and experimental studies to have a good understanding of their properties and Lewis-acid mediated reactivity. At present, it is clear that the nature of framework type (e.g., Ti sites in Beta are suggested to be more acidic than in TS-1[115]) and the type of substituting atom (e.g., Sn is predicted to be of higher acid strength that Ti[116]) play significant roles in determining the nature of the Lewis acid site characteristics. In addition, if reactions are to occur in the presence of water with, ultimately, a bulk water phase, the hydrophobicity of the porous solid must be carefully considered.

A noteworthy characteristic of these Lewis acid centers is that their active tetravalent metals are capable of increasing their coordination sphere by moving from the original framework position to another more-accessible position without becoming separated from the zeolite framework. Under normal circumstances, molecules adsorbed within a zeolite pore cannot interact with the Si^{4+} atom in the center of the $[SiO_4]$ tetrahedron because of the short Si–O distances and the inflexibility of the $[SiO_4]$ species. Fortunately, Ti^{4+}, Zr^{4+}, and Sn^{4+} have larger radii than Si while also exhibiting increased flexibility in their coordination geometry. These two features allow the direct bonding of reagents to the metal atom.[111]

Computational and spectroscopic studies suggest that Sn and Ti atoms exist in two different coordination states in the framework: one consisting of the metal atom tetrahedrally coordinated to O atoms that are each bonded to Si atoms (sometimes denoted the closed site), and the other one having one of the M–O–Si bonds hydrolyzed (sometimes denoted the open site) (see Figure 4). With TS-1, it has been shown that for alkane hydroxylation with aqueous hydrogen peroxide, the active site must be the open site because substitution of the silanol proton with a sodium cation completely eliminates catalytic activity and replacement of the sodium by proton causes the activity to return.[117] Computational studies have also suggested that, energetically, the open site is the more feasible site for catalysis to occur.[92,118−120]

With Sn–Beta, detailed kinetic analyses using MPV and Baeyer–Villiger probe reactions have attributed higher catalytic activity to the site containing a partially hydrolyzed M–OH framework bond.[108,121] Computational studies for Sn–Beta-catalyzed MPV reactions indicate that the Sn–OH group is responsible for initial alcohol deprotonation, yielding an alcoholate intermediate bonded to the Sn center and a water molecule.[111] Although similar studies have not been performed for Zr, it is highly likely that it operates through mechanisms similar to those of Sn and Ti.

CONVERSION OF CARBOHYDRATES USING LEWIS ACIDS IN WATER

2.1. Glucose Isomerization. The isomerization of glucose into fructose is an important industrial reaction used mainly for the production of high fructose corn syrup (HFCS, 8×10^6 tons/yr).[122] In recent years, glucose isomerization has played a crucial role in the synthesis of biomass-derived chemical platforms used for the production of fuels and chemicals.[10,11,123] The reaction is equilibrium limited ($K_{eq} \approx 1$ at 298 K), slightly endothermic ($\Delta H_r = 3$ kJ/mol), and typically catalyzed by an immobilized enzyme (xylose isomerase).[124] Equilibrium mixtures often yield a product distribution of approximately 42% (w/w) fructose, 50% (w/w) glucose, and 8% (w/w) other saccharides.[122] However, although fructose yields are high, the window of operation for this enzyme is very narrow, requiring strict control over reactant purity, reaction temperature, and solvent pH. This drastically limits the cost-effective coupling of glucose isomerization with upstream and downstream biomass processing schemes such as cellulose hydrolysis and carbohydrate dehydration. In this respect, a robust heterogeneous inorganic catalyst would have clear advantages over the biological system.

Homogeneous and heterogeneous inorganic bases are active catalysts for the isomerization reaction at temperatures ranging from 298 to 423 K.[125−127] However, monosaccharides readily decompose into undesirable byproducts in alkaline media at temperatures above 313 K. Thus, high fructose selectivity is obtained only at low conversions or at low temperatures, inevitably resulting in low yields due to kinetic or thermodynamic limitations.[128] Interestingly, higher fructose yields have been obtained from the isomerization of glucose in alkaline media in the presence of ionic species that form Lewis-acid-type complexes with glucose. Early reports on the effects of ion complexation showed that sugars containing an axial−equatorial−axial hydroxyl group sequence on a pyranose ring or a sequence of three cis-hydroxyl groups on a furanose ring shift their mutarotation equilibrium upon interacting with specific cations.[129,130] For example, fructose dissolved in a concentrated solution of $CaCl_2$ showed a shift in its pyranose/furanose ratio from 65:35 to 88:12.[129] The strongest complexes are formed by Ca^{2+}, Sr^{2+}, Ba^{2+}, and the lanthanide cations. For isomerization reactions, yields as high as 80−85% were reported in alkaline solutions in the presence of borate ions, aryl boric acids, and solid poly(4-vinylbenzeneboronate) resins in contact with sodium hydroxide solutions at pH of 12.[131,132]

Similarly, improved fructose yields have been reported in the presence of sodium aluminate and alumina.[133−135] Enhanced yields were attributed to the stabilization of the enediol intermediate through Lewis acid−Lewis base interactions with the aluminum species, resulting in a lower transition state energy for the rate-determining step involving the enediol intermediated.[135−138] A proposed mechanism for glucose isomerization by way of complex formation in the presence of aluminum ions is presented in Figure 5. The first step involves an H-2 hydride shift, followed by the formation of an enediol aluminate complex. Next, cyclization of the enediol occurs by intramolecular bonding of the O-6 or the O-5 to the C-2 of the enediolate, which becomes stabilized as a 1,2-aluminate complex of fructose. In the final step, fructose is obtained by an acid-mediated dissociation of the aluminate complex.[139]

Recently, it was shown that zeolites with the Beta topology that contain tin (Sn−Beta) or titanium (Ti−Beta) metal centers in the framework are highly active catalysts for the glucose isomerization reaction in aqueous media.[113] A glucose solution contacted with a catalytic amount of Sn−Beta at 383 K generated product yields of approximately 46% glucose, 31% fructose, and 9% mannose (see Table 4). Similar product yields were achieved for glucose solutions with concentrations up to 45 wt %. Notably, the Sn−Beta catalyst showed superb stability because it did not show signs of deactivation after multiple cycles or after calcination; no leaching of Sn was detected by elemental analysis; and a hot filtration test showed that the catalysis occurred heterogeneously. Most importantly, the Sn−Beta catalyst was able to perform the isomerization reaction in highly acidic aqueous environments with equivalent activity and product distribution as in media without added acid. This feature enables Sn−Beta to couple isomerizations with other acid-catalyzed reactions.

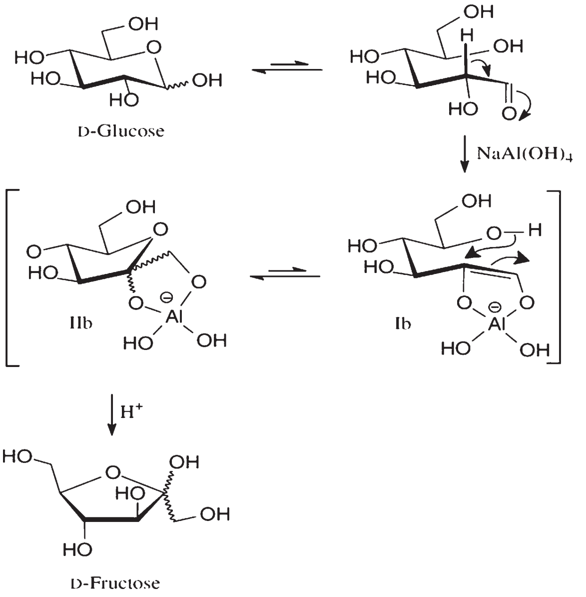


Figure 5. Schematic representation of glucose-to-fructose isomerization in the presence of aluminum ions. From ref 139.

The zeolite topology and the nature of the tin site were shown to drastically influence catalytic activity. The isomerization reaction did not proceed with a medium pore zeolite (MFI), likely due to glucose molecules not being able to enter the smaller pores. Mesoporous stannosilicates (e.g., Sn−MCM-41) were active, but in comparison to Sn−Beta, their activity was considerably lower. The reaction did not proceed when SnO_2, $SnCl_4$, or SnO_2−Beta (created by incorporating SnO_2 nanoparticles into the pores of zeolite Beta) were used.[113,114]

These results indicate that isolated tin sites tetrahedrally coordinated to the crystalline zeolite framework are necessary to catalyze the isomerization of glucose in aqueous media and that the degree of hydrophobicity surrounding the active sites is likely an important parameter to achieve proper reactivity.

A detailed NMR study revealed that Sn−Beta acts as a true Lewis acid during the isomerization of glucose in water.[114] Specifically, using isotopically labeled glucose molecules, it was shown that when Sn−Beta is used as catalyst, glucose isomerization proceeds by way of an intramolecular hydride shift. This hydride shift pathway is similar to the one observed in MPV reactions mediated by Lewis acids involving a six-membered

Table 4. Results for the Isomerization of Glucose in Water[a]

				yield (w/w %)			
entry	catalyst	temperature (K)	time (min)	glucose	fructose	mannose	total saccharides
1	none	383	90	97	0	0	97
2	HCl (p H = 2)	383	90	98	0	0	98
3	Sn−Beta	383	30	45	32	9	86
4	Sn−Beta	413	12	46	30	9	85
5	Sn−Beta/HCl (p H = 2)	383	30	44	33	9	86
6	Ti−Beta	383	90	74	14	5	93
7	SnO_2	383	60	96	0	0	96
8	$SnCl_4$ $5H_2O$	383	60	90	0	0	90
9	Sn−Beta 45 wt % glucose	383	60	46	29	8	83

[a] Reactions were performed with a 10 wt % glucose solution using the corresponding amount of catalyst to maintain a 1:50 metal/glucose molar ratio. From ref 113.

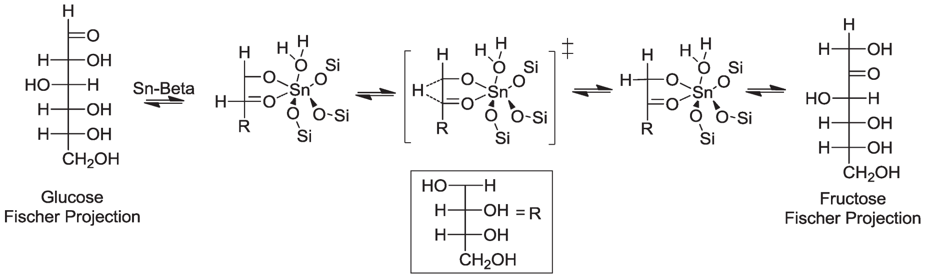


Figure 6. Proposed glucose isomerization reaction mechanism catalyzed by Sn−Beta. From ref 114.

transition state between the metal center, the carbonyl group, and the hydroxyl group in the sugar (see Figure 6).[111,114]

In contrast, a similar spectroscopic study performed with labeled glucose and NaOH showed that the reaction proceeds by way of a proton abstraction and enolization pathway that is typically observed in base-mediated isomerizations.[114] Replacing water with methanol as the solvent resulted in no isomerization activity for Sn−Beta. The lack of activity in methanol is rather intriguing, given that most Lewis acid catalysts perform better in the absence of water. Understanding the intricate interactions among the sugar, the solvent molecules, and the metal center in the zeolite is currently a subject of great interest, and additional studies to address these issues are ongoing within our groups.

2.2. Synthesis of Lactate-Derivatives from Carbohydrates.

Lactic acid (LAC) is an important chemical used widely in the pharmaceutical, food, cosmetic, and chemical industries.[140] Recent growth in demand for LAC, its salts, and its esters has stemmed from their use as platform chemicals for the production of biodegradable polymers and renewable solvents.[141,142] The global market for LAC is predicted to reach 3.3×10^5 metric tons by 2015, taking into consideration existing end-use markets and the emergence of new product applications.[143] Current methods of LAC production are based on the anaerobic microbial fermentation of glucose. The main drawbacks associated with this process are the use of stoichiometric amounts of calcium hydroxide to neutralize the product, the large amounts of energy consumed, and waste generated during the separation of lactic acid from the fermentation broth.[144] Much effort has been devoted to develop efficient chemical synthesis routes to address the drawbacks associated with the biological synthesis route.

Various carbohydrates can serve as feedstock for the production of LAC, including glucose, fructose, xylose, glycerol, dihydroxyacetone (DHA), and glyceraldehyde (GLA), as well as more complex polysaccharides such as cellulose, starch, and sucrose.[145−147] Dissolved metal salts have been used as Lewis acid catalysts for the chemical transformation of these carbohydrates into LAC. For transformation of glucose in water at near-critical conditions, Zn(II), Cr(III), Co(II), and Ni(II) salts generated the best improvement in LAC yields.[145,146] For glucose conversion at temperatures below 140 °C, Al(III) and Cr(II) were identified as the most selective cations for the production of LAC.[148] Interestingly, although reported LAC yields were usually low (<40%) and detailed mechanistic studies were not performed during these investigations, the proposed reaction networks for the production of LAC from C-6 carbohydrates suggested that trioses, such as DHA, GLY, and pyruvaldehyde (PRV), are prevalent intermediate species (see Figure 7). Thus, the conversion of trioses into lactate derivatives has been a subject of intense investigation in recent years.

DHA and GLA can be obtained via biological or chemical synthetic methods from glycerol, a common byproduct from the transesterification of triglycerides used in biodiesel production.[149−153] In view of the interesting results obtained with C-6 carbohydrates, Lewis acid salts have also been investigated for the transformation of these trioses into lactate derivatives. Early reports have shown that transition metal complexes can catalyze this reaction effectively by forming stable Lewis acid−Lewis base complexes in water through chelate substrate binding of the monohydrated

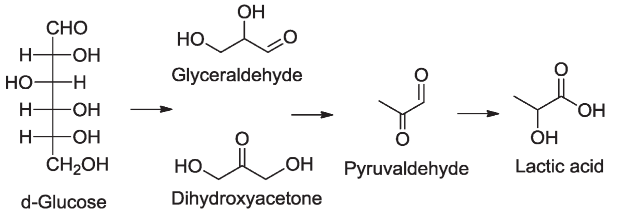


Figure 7. Proposed intermediates in the conversion of glucose into lactic acid.

triose with Rh or Cr species.[154,155] More recently, LAC yields exceeding 90% were achieved starting from DHA using Lewis acid salts containing Al(III) and Cr(III) cationic species.[148,156] In contrast, most other metal salts (e.g., Mn(II),Fe(III), Cu(II), Na(I), La(III), and Sn(II)) were not able to generate the lactate, mainly producing PRV.[156]

It was shown that maintaining the same cation while systematically changing the anion did not result in significant differences in catalyst activity or product selectivity, thereby indicating that anions do not play a significant role in the reaction sequence.[156] When some of these ions were immobilized using ion-exchange resins, it was observed that the best LAC yields were generated by Cr-, Sn-, and Al-containing resins.[157] Mechanistic studies on the aldose—ketose isomerization of GLA to DHA showed that Lewis-acid-mediated isomerization with hydride transfer is strongly catalyzed by added Zn^{2+} cations.[158] Although no spectroscopic data is available to describe the nature of complex formation between the cation and the carbohydrate, these results clearly indicate that specific Lewis-acid-type interactions are required to catalyze the reaction. The identification of such adducts, however, is a challenging task, because the presence of water likely creates a complex and dynamic environment involving multiple hydrated species and aqua ions in solution that slowly deactivate with time.

Replacing water with an alcohol as the solvent during the conversion of trioses generates the corresponding alkyl ester instead of the acid. The use of different solvents has led to a better understanding of the reaction mechanism by allowing the use Lewis acid salts that are unstable in the presence of water. For example, during the conversion of glyceraldehyde in methanol using tin halides, it was observed that almost quantitative yields of methyl lactate were produced.[159] Importantly, it was confirmed that the reaction mechanism involves the transient formation of pyruvic aldehyde prior to esterification.

The large-scale production of lactate derivatives necessitates the use of heterogeneous catalysts to avoid energy-intensive separation procedures. Tin-exchanged hydroxyapatite substrates have been used as supported Lewis acid catalysts in an attempt to replace homogeneous salts in the production of butyl lactates.[160] Although good yields (>73%) are obtained, catalyst deactivation and leaching remain of concern. Recent reports have demonstrated that metallosilicates containing Lewis acid centers are effective and robust catalysts for these transformations.[161] For reactions of DHA in ethanol, amorphous aluminosilicates proved to be the most promising catalysts, generating high ethyl lactate selectivity values (96%) at conversions under 30%. The highest yields (>95%) toward the desired lactate products were obtained with ultrastable zeolite Y materials having a low Si/Al ratio and a high content of extra-framework aluminum.[162,163] It was concluded that both Lewis and Brønsted acidity is required for optimal yield: Brønsted acid sites are needed to convert trioses into PRV, and Lewis acid sites are needed for the intramolecular isomerization of the aldehyde into the lactate. Strong zeolitic Brønsted acid sites need to be avoided because they catalyze the undesired conversion of PRV into alkyl acetals.[163] Under aqueous conditions, however, severe coking and zeolite decomposition were observed.[162]

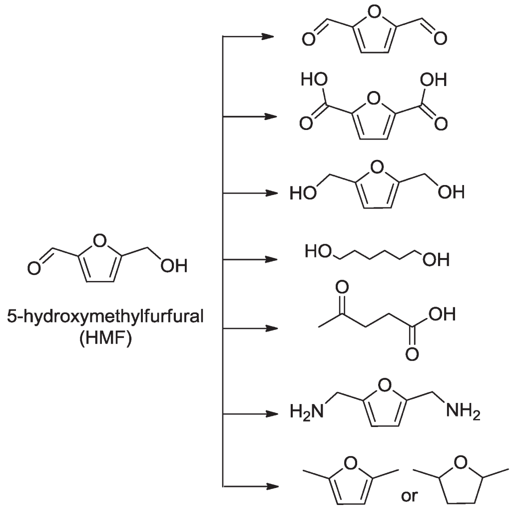


Figure 8. HMF as a platform chemical for production of various chemical intermediates and fuels.

The incorporation of tin into the framework of porous silicates results in highly active and selective catalysts for the production of lactate derivatives from carbohydrates. Sn—Beta catalysts containing small amounts high Si/Sn ratios (typically ranging between 90 and 200) quantitatively convert DHA dissolved in methanol into methyl lactate at 80 °C in 24 h. In the presence of water, LAC yields of 90% can be obtained, but recycling of the catalyst proved to be difficult because the LAC product carbonizes within the zeolite pores (subsequent reuse requires prior calcination to remove this carbonaceous residue).[147,164] Sn—Beta appears to activate the carbonyl and hydroxyl groups in the trioses, promoting an intramolecular hydride shift similarly to that observed for MPV reactions catalyzed by Lewis acids.[147] Investigations on the conversion of GLA into DHA catalyzed by metallosilicates with the Beta topology using density functional and MP2 levels of theory draw attention to three important features: (1) the intramolecular hydride shift is the rate—limiting step in the reaction mechanism; (2) Sn—Beta features the lowest apparent activation barrier for the isomerization reaction when compared to Zr—, Ti— and Si—Beta, with calculated activation barriers in water dielectric medium of 15.4, 23.0, 28.2, and 40.7 kcal/mol, respectively; and (3) a partially hydrolyzed Sn—OH framework bond is required to achieve the lowest energetic barrier for the rate-limiting step (13.8 vs 23.3 kcal/mol for the nonhydrolyzed tin center).[165] Sn—Beta can also convert glucose, fructose, and sucrose into alkyl lactates in an alcohol solution in yields ranging from 45 to 60%.[166] These results suggest that Sn—Beta is also active in breaking the C-6 carbohydrate into two C-3 molecules by way of retro-aldol condensation reactions prior to isomerizing these fragments into the final lactate product.

Mesoporous Sn-MCM41 catalysts showed much faster reaction rates in the production of ethyl lactate from DHA when compared with other tin-containing silicates.[167] Improved reaction rates were attributed to the concerted action of Lewis acid sites with mild Brønsted acid sites located on the surface of the amorphous silica structure.[167] Similar concerted effects between Brønsted and Lewis acid sites have been reported in the conversion of cellulose into lactate derivatives using tungstated aluminum and zirconium oxides.[168] Specifically, these catalysts were capable of transforming 45% of crystalline cellulose into water-soluble species after 24 h at 190 °C. Interestingly, LAC comprised the majority of these soluble species when a tungstated zirconia catalyst was used, whereas much more levulinic acid (a product of HMF hydrolysis) was obtained when sulfated zirconia was used. The drastic change in product distribution was attributed to the varying amounts and types of Lewis and Brønsted acid sites present in each catalyst. A common characteristic among all Lewis acids used was the reduction of the formation of soluble oligomers from cellulose as well as decreased glucose and HMF yields, thereby suggesting that Lewis acids are highly active in the transformation of these intermediates at the reaction conditions used.

Clearly, Lewis acids have a different type of reactivity and effect on product selectivity when compared with Brønsted acids during carbohydrate processing. Further investigations are needed to establish proper structure−function relations for Lewis acids in water. Tunable catalysts in which both Lewis and Brønsted acidity can be controlled in a simple fashion are necessary to establish such relations, ultimately leading to maximum carbohydrate conversion and optimal lactate yields. Recently, materials based on titanium-containing silica beads have been reported as simple and tunable catalysts that are highly active for the transformation of trioses.[169]

2.3. Dehydration of C-6 and C-5 Sugars.

Furan derivatives, such as 5-hydroxymethylfurfural (HMF) and furfural (FUR), are obtained from the selective removal of three water molecules from C-6 and C-5 monosaccharides. These chemicals have been identified as key platform molecules for the production of a wide range of chemicals and fuels from biomass (see Figure 8).[11,170−175] HMF and FUR have been successfully synthesized using a variety of homogeneous and heterogeneous acid catalysts at temperatures typically ranging from 353 to 473 K. Most studies have focused on the dehydration of fructose and xylose in aqueous media, and over 100 inorganic and organic compounds have been used as catalysts for this reaction.[176−180] In most cases, HMF and FUR yields from aqueous fructose and xylose solutions, respectively, range between 40 and 65%. Hydrochloric, sulfuric, and phosphoric acids are the most frequently used inorganic mineral acids, while oxalic, maleic, and *p*-toluene sulfonic acids are the most commonly used organic acids.[176]

Organic and inorganic salts have also been used extensively, including ammonium phosphates, pyridinium, and ammonium sulfate salts, as well as Lewis acidic compounds, including zinc chloride and lanthanum chloride.[177,181−189] When salts have been used as catalysts, detailed descriptions of rate or selectivity enhancements by Lewis-acid-mediated complex formation between the salts and the carbohydrate have not been described in detail. Solid acids, including ion-exchange resins, zeolites, and metal phosphates, have also been used in the dehydration of sugars, generating HMF and FUR yields similar to those obtained with homogeneous catalysts.[179,182,188,190−196] Regardless of the type of catalyst used, the presence of water promotes undesirable fragmentation and condensation reactions when both the furan derivative and the carbohydrate are present in the reaction vessel at elevated temperatures under acidic conditions. For this reason, aprotic solvents,[186,192,197−199] mixed aqueous/organic solvents,[200,201] or biphasic systems[178,179,194,202−207] are typically used to boost product yields by effectively lowering reactant, product, and water concentration, or by separating the product from the reactant into different phases.

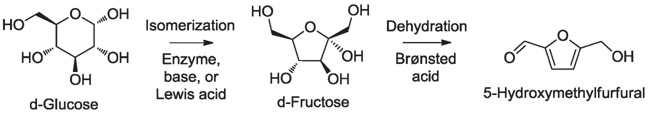


Figure 9. Two-step process for the conversion of glucose into HMF.

The dehydration of glucose, the most abundant sugar in biomass, is preferred over the dehydration of fructose. However, in pure water, glucose dehydration to HMF is extremely nonselective (~6%), leading to the formation of insoluble polymers and several other degradation byproducts.[186,208] Interestingly, although fructose generates quantitative HMF yields in aprotic solvents such as DMSO, HMF yields from glucose in this solvent are much lower (~42% starting from a 3 wt % glucose solution).[199] The direct dehydration of glucose requires harsher conditions (i.e., higher temperatures, longer residence times, and higher acidity) in comparison with those required to dehydrate fructose, thus leading to higher byproduct formation. Differences in reactivity between both sugars have been associated with extreme differences in their pyranose/furanose/open-chain conformation proportions.[129] In glucose, pyranose structures are prevalent, since they have much lower free energies with respect to the other two conformations.[129,209−212] However, various mechanistic studies have emphasized the importance of having high proportions of open-chain or furanose-type intermediates during the initial stages of the reaction.[179,208,213−220] Thus, another contributing factor to lower product selectivities from glucose solutions stems from the additional energy required to convert the sugar into the proper conformation prior to dehydration that may lead to unwanted side reactions.

In addition, sugars heated in acidic aqueous solutions polymerize or self-condense into different types of oligomers (reversion products). The most reactive hydroxyl group of carbohydrates is the hemiacetal or hemiketal hydroxyl group. This hydroxyl group is particularly prone to react with alkyl alcohols to give an acetal or a glycoside.[129] Since sugars are also alcohols with primary and secondary groups, they can initiate the oligomerization process by forming a glycosidic bond with the hemiacetal hydroxyl group from another sugar molecule. When reversible fructose dianhydrides are formed by self-condensation, the most reactive groups for cross-polymerization are internally blocked, thereby reducing parallel reactions during dehydration. Glucose, on the other hand, forms true oligosaccharides that still contain reactive reducing groups that can undergo cross-polymerization with other sugar molecules, intermediates, and the HMF product.[129,177,221] For these reasons, high selectivity for a single species cannot be generally achieved through the direct dehydration of glucose in aqueous media.

An alternative strategy to generate high HMF yields from glucose involves a two-step process whereby glucose is first isomerized into fructose, followed by the dehydration of fructose into HMF (see Figure 9). Combinations of basic Mg/Al hydrotalcites and acidic resins have been used to dehydrate glucose into HMF in dimethylformamide to obtain moderate HMF yields (<45%) at 353 K.[222,223] Higher temperatures resulted in the formation of byproducts and lower HMF selectivity values. Slightly improved HMF yields were obtained by adding the catalysts sequentially (i.e., allowing the isomerization to proceed first before adding the dehydration catalyst). Importantly, the basicity and acidity of each catalyst was maintained after three consecutive runs. A similar approach has been reported using integrated biological and chemical catalyst combinations (xylose isomerase with HCl) in biphasic systems.[224] A sodium tetraborate complexing agent was used to shift the thermodynamic equilibrium in favor of fructose during glucose isomerization to produce HMF yields of ~60%.

Lewis acids can also be potentially used in combination with Brønsted acids to catalyze glucose to HMF cascade reactions. However, water-sensitive Lewis acids used in combination with Brønsted acids in water are expected to have low catalytic activity not only because they progressively deactivate but also because water provides a coordinating polar environment that masks possible complex formation with low-coordinate metal species. For this reason, several studies on carbohydrate dehydration using Lewis acids have focused on systems using ionic liquids as solvents. Although separation of the product from the ionic liquid is often difficult, the use of ionic liquid solvents has the added benefit of preventing many unwanted side reactions (e.g., polymerization, condensation, and rehydration) typically promoted by water, thereby facilitating studies of the reaction mechanism. Thus, ionic liquid systems containing inorganic acids, resins, metal chlorides, heterocyclic carbenes/metal complexes, and mixed salt/solvent/metal chloride mixtures have been used to produce excellent HMF yields from various biomass-derived monosaccharides and polysaccharides while also providing insight into the role of Lewis acid catalysts for the activation of carbonyl groups.[225−237]

Chromium-based salts are widely used because of their superior promoting effects in both activity and selectivity. The chromium metal acts as a hard Lewis acid that forms stable complexes with carbohydrates; these complexes undergo facile isomerization reactions via 1,2 hydride shifts to generate other carbohydrates such as fructose.[238] This effect is augmented when complexes are formed with sugars such as glucose and mannose, but is less pronounced for complexes of galactose, lactose, and tagatose, thereby suggesting that a specific arrangement of hydroxyl groups within the carbohydrate is necessary for proper complex formation. The intrinsic Brønsted acidity of the ionic liquid promotes the subsequent dehydration of fructose into HMF. Interestingly, experimental and theoretical studies on chromium-based ionic liquid systems indicate that dehydration pathways involving binuclear complexes formed by the open-chain conformation of glucose and two Cr centers are more favorable when compared with pathways involving mononuclear complexes.[239] Specifically, DFT calculations show that the transition state for the rate-determining step in glucose isomerization (i.e., the 1,2 hydride shift between C-1 and C-2) is drastically lowered from 120 to 63 kJ/mol when a second Cr center is involved in hydroxide deprotonation.[239] The simultaneous action of two Cr atoms appears to improve negative charge stabilization when electron density is delocalized in the π system during the hydride shift step. Further investigations have recognized that $\mathrm{Cr}^{\mathrm{III}}$ species generate lower energetic barriers than $\mathrm{Cr}^{\mathrm{II}}$ species.[240] These studies clearly indicate that a concerted action of Lewis acid sites on the carbonyl/hydroxyl groups of carbohydrates has a considerable promoting effect on the reaction activity similar to what is observed in enzymatic isomerization systems.[241−243]

The proper formation and stability of Lewis acid complexes is more difficult to predict and control in aqueous environments given the large number of interactions that reactants, intermediates, products, and catalysts have with water molecules. In addition, as described earlier in this review, interaction of water with Lewis acid sites can also generate varying degrees of Brønsted acidity. The complexity of reactive systems using Lewis acids is exemplified by the sharply conflicting reports on the impact of Lewis acidity on the transformation of carbohydrates. Specifically, a detailed study on xylose dehydration using catalysts with varying ratios of Brønsted to Lewis acid sites indicated that Lewis acid sites are responsible of catalyzing most unwanted polymerization reactions. Therefore, it is suggested that the number of Lewis acid sites should be minimized to maximize FUR yields.[244] On the other hand, the use of metal oxides, particularly niobium-based oxides, in water has been reported to improve furanic yields from glucose and xylose, and to enhance hydrolysis rates in the depolymerization of polysaccharides.[245−249] Improved product selectivity has been attributed to the promoting effect from water-tolerant Lewis acid sites located in uncoordinated metal sites within the oxide framework.[247]

Recently, Sn−Beta zeolites have been used in conjunction with homogeneous Brønsted acids in biphasic systems to effectively dehydrate saccharides into HMF.[250] It was observed that Sn−Beta catalyzed a Lewis-acid-mediated isomerization of glucose into fructose, whereas the inorganic acid catalyzed both the hydrolysis of polysaccharides into glucose and the dehydration of fructose into HMF. Surprisingly, Sn−Beta maintained its activity even in the presence of aqueous phases saturated with chloride salts, such as NaCl.[250] In this case, the specific combination of Lewis and Brønsted acid catalysts was shown to benefit glucose conversion toward HMF by efficiently performing a cascade reaction without excessive byproduct formation. Similar beneficial effects of Lewis and Brønsted acid combinations have been demonstrated for the conversion of cellulose into HMF in micellar systems using chromium-based heteropolyacids featuring both types of acid sites.[251] Clearly, further investigations are required to fully understand and exploit possible concerted effects of Lewis and Brønsted acids for biomass conversion processes.

Future Outlook. The activation of carbonyl groups with Lewis acids in aqueous media is undoubtedly an area of research that remains largely unexplored and that offers many opportunities to discover novel chemistry. The vast number of investigations related to chemical transformation mediated by Lewis acids in anhydrous organic media has provided a basic understanding of the intricate dynamics of adduct formation between the acid and the carbonyl moieties and has shed light on the role that these adducts have in accelerating catalytic transformations. A noteworthy example discussed in this review is the dramatic increase in reaction rates for MPV and Michael additions attained by the dual activation of a carbonyl group by two Lewis acid centers placed at particular distances from each other through the formation of bidentate adducts. This effect is analogous to the mode of operation typically observed in enzymatic systems. The recent development of homogeneous water-tolerant Lewis acids has opened the door to apply this knowledge toward the conversion of molecules in the presence of water. However, the majority of these catalysts currently operate via chelation mechanisms, given that the other modes of complexation observed in organic solvents are greatly diminished in the presence of water. Fortunately, as emerging fields featuring complex carbonyl chemistry in aqueous media (e.g., biorefining) become increasingly relevant, new synthetic methods will continue to emerge, giving rise to advanced heterogeneous catalysts capable of forming the same types of adducts as those observed in organic solvents.

Large-scale biomass conversion processes require catalysts capable of operating effectively in the presence of large quantities of water to achieve maximum benefits in terms of cost reduction and process intensification. One reason for this is that biomass feed streams already contain large quantities of water, and another is that most biomass-derived carbohydrates have low solubilities in common organic solvents. In this respect, zeolites containing Lewis acid sites embedded in the framework hold tremendous promise because they have shown excellent activity and stability in the conversion of biomass-derived carbohydrates in aqueous media. In contrast to enzyme-based catalysts, these catalysts appear to be able to process feed streams that do not require strict purification or pH control. The ability to combine these solid Lewis acids with other catalysts may provide ways to perform reaction pathways with numerous steps in single reactors, thus greatly simplifying processing.

The transportation sector, regulated to some extent by environmental mandates, requires fuels with particular quality specifications, including octane number, freezing point, viscosity, vapor pressure, autoignition temperature, among others. These properties are determined by the physicochemical properties of the molecules comprising the fuel. Petroleum refining has developed mature catalytic technologies to generate specific molecular distributions from oil, thus effectively controlling the properties of the fuel. For example, catalytic cracking using acidic zeolite converts long-chain alkanes into shorter branched hydrocarbons that feature an increased octane number and vapor pressure with decreased viscosity. Biofuels are currently being used to replace a portion of fuels derived from petroleum. However, catalytic technologies to transform the highly oxygenated molecules found in biomass into molecules with the proper physicochemical properties are not fully developed. Thus, two critical areas in biomass conversion processes that require our immediate attention are selective deoxygenation and C−C bond forming reactions. The latter are particularly important to upgrade short-chain molecules into fungible fuels that are compatible with current infrastructure. Lewis acids have been shown to be excellent catalysts for C−C bond forming reactions, and we envision that these catalysts, through carbonyl activation, will provide effective avenues for upgrading biomass-derived molecules. Specifically, close attention has to be paid to condensation reaction mechanisms that involve the activation of carbonyl-containing electrophiles, such as aldol condensations and Michael additions. Similarly, activation of carbonyl-containing dienophiles with Lewis acids can lead to enhanced [4 + 2] cycloadditions (e.g., Diels−Alde chemistry) for the production of heterocycles.

Although catalysis with zeolites containing Brønsted acid sites is well established, catalysis with zeolites containing Lewis acid sites is still in its infancy. Therefore, fundamental studies need to be geared at better understanding how to probe and control the nature of active sites. For example, solid Lewis acids require the development of synthetic methods to tune the hydrophobicity surrounding the metal centers as well as to place catalytic sites (both Lewis acid and Lewis bases) at specific locations. Only by achieving a higher level of molecular manipulation within the catalyst structure will we be able to design structures with the precise and well-defined properties necessary to generate targeted molecular distributions from biomass.

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