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Adipic Acid Production via Metal-Free Selective Hydrogenolysis of Biomass-Derived Tetrahydrofuran-2,5-Dicarboxylic Acid

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Abstract

Biomass-derived furans offer sustainable routes to adipic acid (AA), a key chemical in Nylon 6,6 synthesis. In this work, we show that tetrahydrofuran-2,5-dicarboxylic acid (THFDCA) is a viable precursor for AA production, achieving up to 89% yield in a metal-free system containing HI and molecular H_2 in a propionic acid solvent at 160 °C. Reactivity studies demonstrate that the interplay between HI, H_2 , and the solvent is essential for effective THFDCA ring opening. By measuring the reaction orders of HI and molecular H_2 and calculating an acid-base equilibrium constant in a non-aqueous solvent, we show that HI plays a multifaceted role in the reaction by acting both as a proton source and an iodide source to selectively cleave C-O bonds without overhydrogenation of carboxylic acid groups. Using reactivity studies, kinetic measurements, and first-principles computational insights, we demonstrate that metal-free activation of molecular H_2 plays a key role in the reaction, following HI-mediated cleavage of the etheric C-O bond in THFDCA.

1. Introduction

Adipic acid (AA) is an essential commodity chemical used in the commercial production of Nylon 66 and polyurethanes.^{1, 2} AA has been produced almost exclusively from petroleum-derived cyclohexane in an inefficient oxidation process which releases N_2O , a potent greenhouse gas (Scheme 1). In this process, cyclohexane is first oxidized to create KA oil, a mixture of cyclohexanone and cyclohexanol, over Co catalysts (cobalt(II) naphthenate) using air as an oxidant. To maintain high selectivity in this reaction (70 - 90%), the reaction is typically conducted at low conversions (3 to 8%), which necessitates extensive feed recycling and inflated capital costs. AA is then obtained by oxidizing KA oil under harsh conditions using nitric acid, with the production of undesired N_2O .² Tightening regulations on greenhouse gas emissions make the development of renewable and environmentally benign processes for AA production increasingly desirable.



Scheme 1. Commercial AA production from cyclohexane for use as a precursor for 6,6-nylon.²

Biomass-derived 5-hydroxymethylfurfural (HMF) has the potential to replace cyclohexane for renewable AA production, owing to HMF's structure similarity to AA.³ Furthermore, HMF production from biomass has significantly matured with advances in both glucose isomerization to fructose and fructose dehydration to HMF,⁴⁻⁶ thereby paving the way to key commodity chemicals, such as AA. The conversion of HMF to AA requires the oxidation of terminal oxygen-containing groups into carboxyls and the hydrogenolysis/hydrogenation of the furan ring via two possible pathways (Scheme 2): (1) ring opening and hydrogenation of HMF to 1,6-hexanediol (1,6-HDL), followed by oxidation to AA, or (2) oxidation of HMF to 2,5-furandicarboxylic acid (FDCA), followed by ring opening and hydrogenolysis to

AA. The former pathway poses selectivity challenges both in the ring opening step to 1,6-HDL⁷⁻⁹ and in the oxidation of 1,6-HDL.¹⁰⁻¹² Several authors have reported that metal/metal oxide catalysts, e.g., Ir-ReO_x or Rh-ReO_x, can selectively convert 2,5-(bishydroxymethyl)tetrahydrofuran (BHTHF), a hydrogenation product of HMF, to 1,2,6-hexanetriol (1,2,6-HTL) with high selectivity;^{9, 13} however, removing the secondary alcohol in 1,2,6-HTL to make 1,6-HDL is a bottleneck to high conversion and selectivity.⁹ Moreover, total oxidation of two terminal alcohol groups in 1,6-HDL to carboxylic acid groups remains challenging.¹⁰⁻¹² In contrast, the oxidation of HMF to FDCA is quite facile, where yields of >99% can be achieved over Au and Pt catalysts.¹⁴⁻¹⁸ While AA production through FDCA is a promising route, significant work is needed to understand and perform selective FDCA ring opening, e.g., selectively cleaving C-O bonds within the ring, rather than hydrogenating the terminal carboxylic acid groups.



Scheme 2. Proposed pathway to AA from cellulose- and glucose-derived HMF, via (1) via ring opening followed by oxidation (denoted by blue arrows), or (2) oxidation followed by ring opening (denoted by orange arrows). HMF = 5-hydroxymethylfurfural, BHMTHF = 2,5-(bishydroxymethyl)tetrahydrofuran, 1,6-HDL = 1,6-hexanediol, FDCA = 2,5-furandicarboxylic acid, THFDCA = tetrahydrofuran-2,5-dicarboxylic acid, AA = adipic acid.

Boussie et al. proposed that conversion of FDCA can occur through sequential hydrogenation of the furan ring to tetrahydrofuran-2,5-dicarboxylic acid (THFDCA) and ring opening and hydrogenolysis of THFDCA to AA.¹⁹ In the first step, Boussie et al. conducted the hydrogenation from FDCA in acetic acid solvent over noble metal catalysts, such as Pd, at high H₂ pressure (710 psi). In the second step, they performed the hydrogenolysis in a similar manner with the addition of 0.3 M hydriodic acid (HI) to a solution THFDCA in acetic acid. An AA yield of >99% was claimed. In this reaction scheme, the hydrogenation of FDCA to THFDCA is quite facile, occurring at temperatures as low as 40 °C over Pd/Al₂O₃ in a toluene solvent; at such low temperatures, the carboxylic acid groups remained intact.²⁰

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Despite reported high yields of AA from THFDCA, little is known about the underlying reaction mechanism. In particular, the coexistence of HI, H_2 , and the organic acid solvent obscures their respective roles. To this end, we seek molecular level understanding of the ring opening chemistry in order to rationally design this process with less corrosive materials to effectively ring-open THFDCA to AA.

Herein, we present a detailed experimental study, complemented with computational insights, on the ring opening of THFDCA to AA. Reactivity studies show that no metal is needed to facilitate hydrogenolysis of THFDCA in the presence of HI. Instead, HI and H₂ in propionic acid solvent work synergistically to cleave C-O bonds in the THF ring and form the aliphatic diacid, where both solvent choice and proton source are critical. Detailed kinetic measurements show that both H₂ and HI are key in effective ring opening, where H₂ and HI have $\sim 1^{st}$ and $\sim 2^{nd}$ order dependences on the AA formation rate. By combining insights from theory, reactivity data, and kinetic insights using model compounds, we propose that THFDCA ring opening proceeds by HI-mediated ring opening, followed by metal-free activation of molecular H₂ to form AA.

2. Methods and Materials

2.1 Reactivity evaluations

Reactions were conducted in 50 mL stainless steel pressure vessels (Parr Instruments) equipped with a stainless steel thermocouple and Teflon-coated magnetic stir bar. A typical reaction mixture was made by adding the 1 wt% of THFDCA (Carbosynth Ltd., 98%) to a 15 mL mixture of 0.3 M HI (57 wt% in water, Sigma Aldrich) in propionic acid (99%, Sigma Aldrich). Propionic acid, rather than acetic acid, was used as a solvent due to severe overlap between acetic acid and AA peaks in the high performance liquid chromatography (HPLC). Due to the corrosive nature of the reaction mixture, glass inserts were used in the reaction vessel as well as Teflon-coated thermocouples. After collecting an initial sample, the mixture was then added to the glass insert, placed in the reactor vessel, and sealed. The reactor headspace was purged 3 times with N₂ and 3 times with H₂ before pressurizing to the desired reaction pressure. The reactor was subsequently placed over a magnetic stirrer and heated to the desired temperature, regulated

by a PID-controlled ceramic band heater. After the desired reaction time, the reaction was quenched by placing the reactor in an ice bath. Once the reaction mixture was cooled, a sample was collected and stored until analysis in both HPLC and HPLC with on line mass spectrometry (LC-MS). All chemicals were used as received without further purification.

2.2 Analytical techniques

2.2.1 High performance liquid chromatography (HPLC) analysis

Liquid samples, diluted 1:10 with sub-micron filtered water (Thermo Fisher), were analyzed in both HPLC (Alliance Waters System e2695) and LC-MS (Agilent 6120), both equipped with a Bio-Rad Aminex HPX-87H (300 mm \times 7.8 mm) column. The HPLC method was optimized, using 0.50 mL/min of mobile phase (5 mM H₂SO₄) with a column temperature of 50 °C. For LC-MS, a mobile phase of 1% formic acid was used instead of 5 mM H₂SO₄ for compatibility with the mass spectrometer. Conversions and yields were calculated using the following equations:

$$X_i = \frac{C_{i,0} - C_{i,\text{final}}}{C_{i,0}} \cdot 100\% \ (1) \qquad \qquad Y_j = \frac{C_{j,\text{final}}}{C_{i,0}} \cdot 100\% \ (2)$$

where X_i and Y_j correspond to conversion of reactant *i* and yield of product *j*, respectively, $C_{i,0}$ is the initial concentration of the reactant *i* (mol L⁻¹), $C_{i,\text{final}}$ is the final concentration of the reactant *i* (mol L⁻¹), and $C_{j,\text{final}}$ is the final concentration of a product *j* (mol L⁻¹). Concentrations were measured by integrating peaks HPLC chromatograms which were calibrated based on prepared solutions of known concentration.

2.2.2 Inductively-coupled plasma mass spectrometry (ICP-MS)

Quantification of trace metals in the solution was conducted using an inductively-coupled plasma mass spectrometer (ICP-MS). Trace metal standards containing 100 μ g/mL Au, Pt, Pd, Ir, Ru, Rh, Cr, Fe, and Ni in 5% HCl, were obtained from High-Purity Standards. These solutions were diluted in 2% HCl to solutions of varying known concentrations for accurate calibration. ICP-MS samples of stock HI were prepared by diluting stock HI in 2% HCl by a factor of 100. ICP-MS samples from post-reaction mixtures were obtained by reacting 0.3 M HI (no THFDCA) in 15 mL propionic acid under 500 psi H₂ pressure for 2 h at 160 °C. Because organic compounds are incompatible with the ICP-MS, the solvent was removed by allowing the post-reaction solution to stir via magnetic stir bar over a hot plate set to ~100 °C in a

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ventilation hood. After about 4 h, the solvent was completely removed. The remaining solid was washed with water and again left to evaporate at ~40 °C to ensure that all organic matter was removed; this was repeated 3 times. After the final washing and evaporation step, 15 mL of water was added and stirred vigorously to dissolve all the remaining solid. This mixture was then diluted 1:10 in 2% HCl and injected into the ICP-MS for quantitative analysis.

2.3 Scanning electron microscopy with X-ray microanalysis

Scanning electron microscopy (SEM) with X-ray microanalysis (SEM-EDX) was conducted on a Joule 7400 instrument equipped with Inca X-ray microanalysis. Samples were prepared by evaporating the solvent, vented to a ventilation hood. The solid was collected and placed on carbon tape prior to SEM-EDX analysis. EDX was conducted with an electron energy of 25 keV.

2.4 Kinetic modeling of tetrahydrofuran-2,5-dicarboxylic acid (to adipic acid) and malic acid (to succinic acid) hydrogenolysis

Kinetic models were created to describe time-dependent data of the ring opening of THFDCA to AA as well as the hydrogenolysis of malic acid (MA), a model compound, to succinic acid (SA) in the presence of HI and H₂ in propionic acid solvent. In describing MA hydrogenolysis, we compared two reaction networks: a two-step dehydration-hydrogenation mechanism via fumaric acid (FA), referred to as Model A, and a combination of dehydration-hydrogenation and a direct C-O bond hydrogenolysis to form SA in a single step (model B; Scheme S1). Both models contained a reversible esterification reaction between MA and the propionic acid solvent to form 2-(1-oxopropoxy)butanedioic acid (BEA). THFDCA hydrogenolysis network, referred to as Model C, included three reactions: ring opening of THFDCA to 2hydroxyadipic acid (HAA), hydrogenolysis of HAA to AA, and esterification of HAA with the solvent to form 2-(1-oxopropoxy)hexanedioic acid (PEA; Scheme S1). No iodine-containing species were included in models, since they were not observed in any time-resolved experiment. Regression/estimation of rate constants was conducted in MATLAB's Optimization Toolbox using the lsqnonlin function. Full model details, including derivations and equations, can be found in the Supplementary Information (Section S1).

2.5 Ab initio reaction energetics

Gibbs free energies of THFDCA-pertinent reactions and HI acid dissociation constants were calculated using the Gaussian 09 software package²¹. Selected basis sets were obtained from the EMSL Basis Set Library^{22, 23}. Due to both neutral and charged species involved, we employed a composite computational scheme inspired by Shields and co-workers^{24, 25}, in which gas phase energies and solvation energies are calculated at different levels of theory. The method was proven to be successful for accurate pK_a estimates of acids.²⁵ Solvation contributions to Gibbs free energies of acid deprotonation and THFDCA ring-opening reactions were essential to explain the role of acid nature and the solvent mixture composition on AA yields. All molecules were pre-optimized in the gas phase at the restricted Hartree-Fock (RHF) level of theory, using the 3-21G basis set,^{26, 27} Vibrational frequencies were calculated using density functional theory,^{28, 29} M06-2X exchange-correlation functional,³⁰ and the LANL2DZ basis set,³¹⁻ ³³ following the geometry optimization at the same level of theory. We employed the Def2-TZVPD basis set³⁴ for accurate structure and electronic energy calculations, as it contains diffuse basis functions, crucial for description of anions. Gibbs free energies of solvation were computed as an energy difference between the molecule in the gas phase and in the implicit solvent, calculated at the RHF/6-311G³⁵⁻³⁹ level of theory with geometry optimizations. No geometry optimization in the solvent was performed for cationic species (H_3O^+ , protonated THFDCA), due to convergence difficulties. The implicit solvent was modeled using the conductor-like polarizable continuum model (CPCM).^{40, 41} A solute cavity was specified using the United Atom Topological Model applied on radii optimized for the HF/6-31G(d) level of theory (UAHF). We employed the 6-311G instead of 6-31G(d) basis set, used in the original CPCM parameterization,⁴⁰ as the former was available for all chemical elements utilized in this study, including iodine. We used acetic acid (HAc) as a surrogate for propionic acid, due to availability of HAc experimental data^{42, 43} for method benchmarking, which is justified by the similar AA yields achieved in HAc and propionic acid solvents. Co-solvent (H₂O) effects on the HAc dielectric constant are neglected in this study, unless noted otherwise.

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In order to validate the composite method for our solvent and the basis set choice, in Table S1, we compare the computed acetic acid self-dissociation constant (K = $[H_2Ac^+]$ Ac⁻], corresponding to 2HAc \rightarrow H₂Ac⁺ + Ac⁻) with its experimental value (1.2×10⁻¹⁹ at 105.7 °C⁴²). The CPCM-UAHF/RHF/6-311G method predicts the autoprotolysis constant to be 2.6×10^{-20} , which is less a factor of 5 smaller than the experimental value. For comparison, a commonly employed semi-empirical SMD implicit solvation model⁴⁴ at the M06-2X/Def2-QZVPD level of theory predicts it to be 8 orders of magnitude lower $(6.2 \times 10^{-27}).$

In order to calculate the HI acid dissociation constant in an organic acid (glacial acetic acid; $pK_{HI,HAC}$), we developed a computational scheme that requires the following properties as an input: HAc experimental self-dissociation constant $pK_{HAC,HAC}$, HI and HAc experimental acid dissociation constants in water $(pK_{HI,w}, pK_{HAC,w})$, and calculated solvation Gibbs free energies of HI, I⁻, HAc, and Ac⁻ species. The scheme benefits from cancellation of errors and eliminates H_3O^+ (as well as H_2Ac^+), known to be poorly described by the implicit solvent model. In Scheme 3 we depict two thermodynamic cycles outlined in Section S3. HI acid dissociation constants are calculated according to Equations (1a) and (1b); the notation corresponds to Scheme 3.

(a)

(a)

$$HI_{gas} \xrightarrow{pK_{HI,gas}} H_{gas}^{+} + I_{gas}^{-} \qquad (b)$$

$$HI_{gas} \xrightarrow{pK_{HI,gas}} H_{gas}^{+} + I_{gas}^{-} \qquad HI_{gas} \xrightarrow{pK_{HI,gas}} H_{gas}^{+} + I_{gas}^{-} \qquad HI_{gas} \xrightarrow{pK_{solv,}} PK_{solv,} \qquad PK_{solv$$

Scheme 3. Thermodynamic cycles used to derive the HI pK_a expression. (a) HI acid dissociation in water (w). (b) HI dissociation in acetic acid (HAc). pK values are related to Gibbs free energies ΔG of the corresponding processes as $pK = \Delta G/2.303RT$, where R is the gas constant, T is temperature.

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$$pK_{HI,HAc} = pK_{HAc,HAc} + (pK_{HI,w} - pK_{HAc,w}) + \Delta pK_{solv,I-} - \Delta pK_{solv,HI} - \Delta pK_{solv,Ac-}$$
(3a)
+ $\Delta pK_{solv,HAc}$

$$\Delta p K_{solv,i} = p K_{solv,i/HAc} - p K_{solv,i/w}$$
(3b)

We benchmarked the pK_a computational scheme against experimental pK_a of HCl, HBr, H₂SO₄, and HClO₄ in glacial acetic acid; the data are reported in Table S2. Errors in predicted pK_a values are less than 1.1 pK_a unit for HCl, HBr, and H₂SO₄. Success of the implicit solvation scheme indicates that the previously hypothesized ion pair formation after acid dissociation in glacial acetic acid⁴³ does not occur to a significant extent.

To calculate the equilibrium constant of the H_2O -assisted HI dissociation in acetic acid containing water impurity, we first obtain an estimate of the H_3O^+ solvation energy, known to be poorly described by the implicit solvent model. We exploit the Br/I similarity and use the experimental HBr dissociation constant in the HAc solvent with water impurity,⁴³ together with a range of experimental and computed properties (see Section S4, Tables S3 and S4). We find the Gibbs free energy of H_3O^+ solvation in acetic acid to be equal to -113.84 kcal/mol; the corresponding value in water, obtained using a similar method, is -114.06 kcal/mol, i.e., the model predicts similar H_3O^+ solvation energies in H_2O and $HAc+H_2O$ impurity. For comparison, the experimental H_3O^+ solvation energy in water is -103.4 kcal/mol.⁴⁵ We note that two most successful methods for pK_a calculations (CPCM⁴⁶ and COSMO-RS⁴⁷) systematically overestimate ion solvation energies, leading to H_3O^+ solvation energy overestimation, with a minor effect on pK_a results. We calculate the HI pK_a in water to be equal to -9.70, in excellent agreement with the experimental value (-10), validating this approach.

In order to calculate an equilibrium constant of H_3O^+ + THFDCA \rightarrow H_2O + THFDCA· H^+ over a range of water concentrations, we utilize the experimentally measured dielectric constant dependence on the HAc/H₂O mixture composition (Figure S1),⁴⁸ as an input to the CPCM model. Although absolute

 H_3O^+ (and probably THFDCA·H⁺) solvation energy cannot be accurately calculated by this method, successful application of the Born equation to describe pK_a variations in water/alcohol mixtures⁴⁹ indicates that composition-dependent acid dissociation trends can be well described by the implicit solvent model (Section S5, Tables S5-S7).

3. Results and Discussion

Table 1. Reactivity data from THFDCA at 160 °C

	Acid	Catalyst	<i>P</i> _{H2} (psi)	Solvent	Time (h)	Conversion (%)	Y _{AA} (%)
1	0.3 M HI	None	500	Propionic acid	2	99	89
2	0.3 M HI	Pd/C	500	Propionic acid	2	99	82
3	None	None	500	Propionic acid	2	0	0
4	0.3 M HI	None	None	Propionic acid	2	0	0
5	0.3 M HI	None	500	Water	2	3	0
6	0.3 M HI	None	500	2-propanol	2	<1	<1
7	0.3 M HBr	None	500	Propionic acid	2	24	14
8	0.3 M HCl	None	500	Propionic acid	2	32	3
9	$0.3 \text{ M} \text{H}_2 \text{SO}_4$	None	500	Propionic acid	2	16	<1
10	0.3 M HClO ₄	None	500	Propionic acid	2	11	<1
11	0.3 M H ₂ SO ₄ + 0.3 M LiI	None	500	Propionic acid	2	12	<1
12	0.3 M HClO ₄ + 0.3 M LiI	None	500	Propionic acid	2	24	<1
13	0.3 M H ₂ SO ₄ + 0.3 M LiI + 1.8 M H ₂ O	None	500	Propionic acid	2	9	<1

Conditions: 1 wt% THFDCA in 15 mL propionic acid.

3.1 Metal-free ring opening in organic acid solvents

Though metals or metal oxides are typically necessary to catalyze hydrogenolysis reactions, effective ring opening of THFDCA to AA occurs facilely in the absence of a metal catalyst when HI and H₂ are employed in organic acid solvents. In the presence of Pd/C, 500 psi H₂, and 0.3 M HI in propionic acid, full conversion of THFDCA was achieved after reaction at 160 °C, forming ~82% yield of AA, consistent with a recent patent.¹⁹ Surprisingly, full conversion and slightly higher AA yield (89%) was reached in the absence of Pd/C under otherwise identical conditions, indicating that hydrogenation or hydrogenolysis reactions occur in the presence of HI and H₂ without Pd-mediated hydrogen activation (Table 1, entries 1-2). Control experiments indicate that ring opening is only effective when all three of HI, H₂, and propionic acid are employed simultaneously. Removing one of the compounds results in complete loss in activity at 160 °C (Table 1, entries 3-5), which raises several questions: (1) the role of HI, (2) the nature of H₂ activation, and (3) the role of the organic acid solvent. Below we address these questions via systematic reactivity, computational, and kinetic modeling studies.

3.2 Effect of hydriodic acid on THFDCA ring opening

3.2.1. Experimental assessment

HI plays a unique role in THFDCA ring opening, which likely stems from both HI's strong acidity and iodide's direct participation in the reaction. To access the role of HI's acidity, we systematically explored the impact of alternative sources of proton and iodide on THFDCA conversion. The effect of proton was investigated by replacing stock HI ($pK_a \sim -10$; all pK_a values are defined in an aqueous solution unless noted otherwise, 57 wt% HI in water)⁵⁰ with other strong acids, e.g., 70 wt% HClO₄ in water ($pK_a \sim -10$) and 99.99 wt% H₂SO₄ ($pK_a \sim -3$ for the first proton, ~2 for the second proton),⁵⁰ in the absence of iodide. Doing so resulted in a stark decrease (99% vs. 11% and 16%, respectively) in conversion and negligible AA yield (Figure 1a) under identical conditions as compared with HI, suggesting that the acid strength alone cannot explain the effectiveness of HI in the ring opening of THFDCA. Using other hydrohalic acids, e.g., HBr ($pK_a \sim -9$) and HCl ($pK_a \sim -7$),⁵⁰ in place of HI

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again resulted in a significant loss in activity when compared with HI (Figure 1a, 99% conversion vs. 24% and 32%, respectively), where the AA yield decreases in the sequence of HI > HBr > HCl (Figure 1a). This relationship parallels the acid strength of each of these acids, suggesting that protonation of THFDCA could play a key role in ring opening. Additionally, the sequence also parallels the halides' nucleophilicity in polar protic solvents, where iodides are the strongest nucleophiles.⁵¹ Increasing HI concentration positively impacts the AA formation rate (Figure 1b). Furthermore, analysis of the initial AA formation rate (at THFDCA conversions <15%, see Section S6 and Table S8) at 100 °C versus HI concentration results in a slope of 1.6 ± 0.1 , suggesting that the reaction order with respect to HI is close to 2^{nd} order. This is consistent with the reaction orders previously proposed for ether bond cleavage by hydrogen halides,^{52, 53} where HI was used to cleave the C-O bond in various alkyl ethers to an alcohol and an iodoalkane. No detectable conversion of THFDCA was observed in the absence of HI at 100 °C after 4 h, demonstrating that HI's participation is critical.

Just as HI's acid strength cannot fully explain its high activity, the iodide component alone cannot account for HI's performance. When a solution of 0.3 M lithium iodide (LiI) in propionic acid was used as a substitute for 0.3 M HI in propionic acid at 160 °C, THFDCA remained unreactive, confirming the importance of protons in driving the ring opening reaction. Adding a strong acid to a mixture of THFDCA and LiI in propionic acid still cannot reproduce the conversion and yield obtained with stock HI. This is evidenced by reactions with 0.3 M LiI and 0.3 M H₂SO₄ or HClO₄ in propionic acid, forming no appreciable AA (<1%) at <25% THFDCA conversion in both cases under otherwise identical conditions (Table 1, entries 11 and 12). Adding iodide and proton components separately, e.g., H₂SO₄ and LiI, may not be representative of adding HI, because the stock HI solution contains 43% water by weight. Thus, a 0.3 M HI solution in propionic acid intrinsically results in a water concentration of 1.8 M in the final reaction mixture. To test the role of water, 0.48 g water was added to a propionic acid mixture containing 1 wt% THFDCA, 0.3 M LiI, and 0.3 M H₂SO₄ to mimic the water concentration when HI is added; again, no appreciable AA formation was observed as compared to the case with HI (Table 1, entry 13). Although employing HBr in place of HI results in a decrease in AA yield (14% vs. 87%, Table 1),

the production of AA from HBr and HI suggests that the halide component is critical, where either the nucleophilicity of the halide, the strong acidity, or both, could explain the performance of hydrohalic acids over other mineral acids. These experiments suggest that a physical mixture of an iodide source and a proton source (aside from the solvent) is not equivalent to HI. This could be due to the degree of dissociation of mineral acids, which is dependent on the nature of the solvent (Leveling effect).^{54, 55} Computations, discussed next, shed light on the acid dissociation trend in an organic acid solvent.



Figure 1. Effect of acid at 160 °C after 2 h on the THFDCA conversion and AA yield (a) and effect of varying HI concentration at 100 °C after 4 h on the AA production rate (b). Conditions: 1 wt% THFDCA in 0.3 M HI under 500 psi H_2 .

3.2.2. Theoretical modeling of dissociation constants

To calculate HI's acid dissociation constant in an organic acid (glacial acetic acid; $pK_{HI,HAc}$), we used the computational scheme outlined in the section 2.5. The calculated HI pK_a value for the HI + HAc \rightarrow H₂Ac⁺ + I⁻ process is 4.65, indicating that HI is a weak acid, and H₂Ac⁺ ions are unlikely to participate in the THFDCA ring-opening chemistry due to their negligible concentrations.

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As the HI stock solution contains $\sim 7 \text{ mol}\%$ of water, we propose that HI dissociation is primarily H₂O-assisted, corresponding to HI + H₂O \rightarrow H₃O⁺ + I⁻, where all species are solvated by the organic acid. The H₂O-assisted HI dissociation constant, defined as $K_a = [H_3O^+][\Gamma]/[HI][H_2O]$, is calculated to be equal to 440, or $pK_a = -2.6$, at 298.15 K, significantly greater than the HAc-mediated dissociation constant, reported above. For comparison, experimental H₂O-assisted K_a of HClO₄, HBr, and H₂SO₄ in acetic acid are 27.8, 14.1, and 4, respectively.⁴³ Larger K_a 's in the presence of water are consistent with the significant increase in conductances of HCl and H₂SO₄ in acetic acid solutions upon water addition,⁵⁶ due to their increased dissociation extent. We note, however, that the reported absolute values of calculated and experimental K_a 's cannot be used to calculate the acid-dependent concentration of catalytic protons in the THFDCA reaction system, since they correspond to much lower acid and water concentrations in HAc $(5 \cdot 10^{-3} \text{ M} \text{ and } 0.067 \text{ M}, \text{ respectively}^{43})$. As to the relative magnitudes of K_a 's, the comparison is complicated by ion pairs, potentially formed in solvents with low dielectric constants (acetic acid, $\varepsilon = 6.25$; propionic acid, $\varepsilon = 3.44$), due to incomplete screening of electrostatic interactions. The indicator-based K_a measurement method⁴³ is not sensitive to ion pair formation, and thus the reported K_a 's may not reflect the true availability of protons for catalysis. However, we ruled out ion pair formation in H_2SO_4 , HCl, and HBr solutions in glacial HAc by reproducing their conductance-based experimental pK_a values within 1 unit, as we assumed non-interacting ions in the implicit solvent model; the reported dissociation constants (as well as the HI dissociation constant by analogy with HBr) most likely reflect their true relative acid strengths. HClO₄ dissociation constant is an exception: conductance studies indicated the formation of H_2Ac^+ ·ClO₄⁻ ion pairs in the HClO₄/HAc solution,⁵⁶ consistent with inability of the implicit solvent method to reproduce the $HClO_4$ dissociation constant in glacial HAc (Table S2). In addition, ion pair formation leads to only a weak increase in the HClO₄/HAc solution conductivity upon water addition,⁵⁶ i.e., H₂O does not promote HClO₄ dissociation as efficiently as it does for other acids. We conclude that in the THFDCA reaction system, acid dissociation constants follow the trend HI>HBr>H₂SO₄>HClO₄; a similar trend holds for their corresponding activity in AA production, even when LiI is present. The correspondence between acid strengths and AA yields is consistent with the

Brønsted acid-catalyzed ring-opening mechanism driven by HI dissociation, in which catalytically active protons are bound to water molecules.

3.4 Effect of hydrogen and THFDCA on ring opening activity

THFDCA conversion and AA yield grow linearly with H₂ pressure in the presence of 0.3 M HI in propionic acid solvent (Figure 2a), suggesting that hydrogen plays an important part in AA's formation. When no hydrogen is used (500 psi N₂), THFDCA remains unreacted in the temperature range of 100 to 160 °C after 4 h of reaction. At 115 °C, the formation rate of AA increases linearly with increasing H₂ pressure in the range of 50 to 500 psi at low THFDCA conversions (<20%, see Section S6 and Tables S9 and S10). Plotting $\ln(r_{AA})$ versus $\ln(P_{H2})$ results in a roughly linear relationship with a slope of ~0.9 ± 0.1 (Figure 2a), which is close to 1st order with respect to H₂. By a similar procedure, a first-order dependence in THFDCA concentration is observed (a slope of 0.9 ± 0.1, Figure 2b). The strong correlation between AA yield and H₂ pressure in the presence of HI (Figure 2a) suggests that H₂ actively participates in the reaction in the absence of any metal catalyst. To confirm that hydrogen is activated in the absence of metal catalysts, two possibilities need to be ruled out: (1) trace metal contaminations, introduced *in situ* or from commercially available chemicals, dissociate molecular H₂ to perform the reaction or (2) HI mediates the necessary hydrogenolysis reactions by assisting in H₂ activation.



Figure 2. Effect of each reactant on AA formation rate: (a) effect of H₂ (50, 100, 200, 300, and 500 psi) using 1 wt% THFDCA in propionic acid and (b) effect of THFDCA concentration (0.1, 0.5, 1, 2 wt%) under 500 psi H₂. Conditions: THFDCA in a mixture of 0.2 M HI in propionic acid at 115 °C, t = 4 h.

Elemental analysis of stock HI via ICP-MS revealed no significant transition metal species. This is evidenced by comparing a diluted stock HI mixture from Sigma-Aldrich (0.1%) with a high purity standard, containing the most common transition metals capable of activating molecular H₂, including Pt, Pd, Ir, Ru, Rh, Ni, Cu, Fe, and Cr. For each element tested, levels remained below the detection limit of the instrument, thereby ruling out the possibility that stock HI directly introduces metal contaminants to the reaction mixture.

Elemental analysis of post-reaction mixtures showed evidence of the metal species, such as Fe, Cr, and Ni, the presence of which could facilitate hydrogen activation. Samples were prepared by removing the solvent from a post-reaction mixture of THFDCA, 0.3 M HI, and 500 psi H₂ in propionic acid at 160 °C for 2 h. Removal of solvent was conducted via controlled evaporation at 100 °C until only solid species remained. Then, the resulting solids were dissolved in pure H₂O, diluted, and analyzed by ICP-MS. Elemental analysis of solids in SEM-EDX revealed that both Fe and Cr were present in the dried

sample with a mass ratio of ~4:1. A similar ratio was observed by ICP-MS, where Fe and Cr was detected at concentrations of 255 ppm and 63 ppm Cr, respectively (ratio ~4:1). Ni was also detected via ICP-MS with a concentration of 202 ppm, where Cu, Mn, and Co levels remained < 20 ppm. The Fe:Cr ratio strongly suggests that these metal species originate from the stainless steel of the inner walls of the reaction vessel. Although glass inserts were used in the stainless steel reactors, vapor-phase HI and/or propionic acid likely condense onto the inner walls of the top of the reactor due to their volatility and leach metals into the reaction mixture. This provides a source of metal contamination in the reaction system, which could provide metal sites for H_2 activation. To test this possibility, mixtures containing ~0.05 M Fe, Ni and Cr salts (major metal components detected by ICP-MS), e.g., FeBr₃, Ni(NO₃)₂, and $CrCl_3$ ·6H₂O, and 1 wt% THFDCA in propionic acid were employed in reactions under 500 psi H₂ (no iodide source). We used metal salt concentrations significantly larger (0.05 M) than the concentration of Fe detected by ICP-MS (255 ppm or ~ 0.005 M) to verify whether these metals play an active role in the chemistry. After reaction with no iodide source, minimal activity was observed at 115 °C after 4 h (Figure 3, red bars). However, when 0.3 M LiI was added to CrCl₃·6H₂O, a significant increase in AA formation rate was observed as compared to that when no iodide was used (Figure 3, green bars). Iron salts, e.g., FeBr₃, do not show enhanced activity when iodide was added (Figure 3, green bars). Furthermore, increasing the CrCl₃·6H₂O concentration from 0.05 to 0.15 M, results in increased AA formation rate, suggesting that CrCl₃ promotes the ring opening chemistry in the presence of LiI. Despite the promising synergy displayed by the combination of Cr and iodide, the observed activity cannot match that when 0.3 M HI is used. Insignificant role of Cr, Fe, and Ni in hydrogen activation is further supported by experiments, where $CrCl_3 \cdot 6H_2O_5$, FeBr₃, or $CrCl_3$ were added to reaction mixtures containing 0.3 M HI (blue bars, Figure 3), in which no detectable increase in AA rate was achieved within the experimental error. To confirm that it is not synergy between Cr^{3+} and proton, rather than iodide, CrCl₃·6H₂O was added to 0.3 M H₂SO₄ resulting in only minimal AA yield (Figure 3, orange bars). In summary, our control experiments show that the metal contaminants are unlikely to play any major role in H₂ activation.





Figure 3. AA formation rate in the presence of Cr, Ni, and Fe salts alone (red bars), 0.3 M HI (blue bars), 0.3 M LiI (green bars), and 0.3 M H₂SO₄ (orange bars). Three concentrations (200, 500, and 800 mg) of $CrCl_3 \cdot 6H_2O$ were plotted from bottom to top in the presence of LiI. Conditions: 1 wt% THFDCA in 15 mL propionic acid at 115 °C for 4 h, $m_{salt} = 200$ mg which corresponds to ~0.05 M of the metal.

3.4 Impact of solvent on the cleavage of THFDCA's ether bond

3.4.1 Experimental assessment

The solvent plays a profound role in THFDCA ring opening. Among the tested solvents, only organic acid solvents, i.e., acetic acid and propionic acid, are viable candidates for ring opening of THFDCA. Water or 2-propanol are poor solvents, each resulting in <1% AA yield under otherwise identical conditions, in stark contrast to the >80% AA yields obtained in organic acids (Figure 4a). To understand the role of water in the reaction, the concentration of water in propionic acid was systematically varied in the reactant mixture. Because HI is employed in its aqueous solution (57% HI by weight), adding HI inherently introduces water to the reaction mixture. Water concentration in the reaction mixture is captured by the bottom axis in Figure 4b, and the volume of water added in excess to that from HI is shown in the top axis. The water concentration from the stock HI solution is 1.1 M. As the water concentration varies between ~1.1 to 2.7 M (0 to 0.4 mL of added H₂O), the THFDCA conversion

and the AA yield are not significantly affected (~39-45% and 30-36%, respectively). This indicates that the results from the HI concentration dependence experiments (Figure 1b) are unlikely influenced by the varying water concentration in any significant manner. However, further increasing water concentration to 8.5 M resulted in a significant decrease in THFDCA conversion and AA yield. Once water concentration exceeds 8.5 M, AA formation becomes too slow to observe over the 4 h reaction time. Thus, at high concentrations, water plays a strongly inhibitive role in ring opening.



Figure 4. Solvent effects on AA yield: (a) conversion and yield in each solvent (0.3 M HI) at 160 °C for 2 h; (b) effect of water concentration in propionic acid at 115 °C for 4 h (0.2 M HI). Conditions: 1 wt% THFDCA under 500 psi H_2 .

ACS Catalysis

Water's ability to suppress AA production is likely associated with interference of the H₂O (the strongest base in the system) with the acid-catalyzed THFDCA ring-opening mechanism. HI has been shown to catalyze the cleavage of ether bonds effectively by addition of proton and iodide across the C-O bond to form an iodoalkane and an alcohol, e.g., converting diethyl ether to iodoethane and ethanol (Scheme 4a and 4b).^{52, 53} The ether bond breaking proceeds by protonation of the oxygen atom to form an oxonium cation (Scheme 4c),⁵³ followed by halide addition and release of an alcohol fragment via S_N1 or S_N2 -type reactions (Scheme 4c, pathways (1) and (2), respectively), with S_N2 being the dominant one for ethers with adjacent primary or secondary alkyl groups.⁵³ At high HI concentrations the alcohol product undergoes subsequent conversion to an iodoalkane by nucleophilic substitution (Scheme 4b).⁵⁷ A similar



Scheme 4. Ether bond scission mechanisms showing (a) general ether bond scission by HI, (b) diethyl ether bond scission by HI, (c) S_N1 (1) vs. S_N2 (2) pathways for ether bond scission of 2-methoxypropane, (d) ether bond scission of THFDCA by HI, (e) inhibition of ring opening via water's basicity. THFDCA = tetrahydrofuran-2,5-dicarboxylic acid, IHA = 2-iodo-5-hydroxyhexanedioic acid.

oxonium-mediated C-O bond breaking mechanism in THFDCA is consistent with the acid strength dependence of the AA formation rate (Figure 1a). THFDCA protonation leads to oxonium, referred to as THFDCA \cdot H⁺, that is likely to be strongly acidic, with pK_a values similar to that of dimethyl ether (-3.8 in aqueous H₂SO₄⁵⁸) or tetrahydrofuran (-2.1).²⁷ Subsequent iodide-mediated ring opening is proposed to form 2-iodo-5-hydroxyhexanedioic acid (IHA), which is not detected in the products, likely due to the fast subsequent hydrogenolysis step of the C-I bond to form HAA (vide infra; Scheme 4d). Due to strong THFDCA \cdot H⁺ acidity, at high water concentration protonation of THFDCA could be suppressed in favor of hydronium formation, because water acts as the strongest base (Scheme 4e). Below, we quantify the relative basicity of THFDCA and water in an organic acid solvent using first principles calculations.

3.4.2. Theoretical insights into water's role in ring opening of THFDCA

By employing the pK_a difference between protonated dimethyl ether and hydronium ion in water as a reference ($\Delta pK_a = 2.1$, calculated from dimethyl ether pK_a = -3.8⁵⁸ and hydronium pK_a = -1.7), we compute the THFDCA protonation reaction (H₃O⁺ + THFDCA \rightarrow H₂O + THFDCA·H⁺) to be exoergonic



Figure 5. Experimental adipic acid yield and predicted protonated THFDCA molar fraction as a function of water molar fraction. Highlighted green and olue areas indicate ranges of H_2O molar fractions that correspond to exoergonic and endoergonic THFDCA protonation, respectively.

 $(\Delta G = -1.04 \text{ kcal/mol} \text{ at } 25 \text{ °C})$ at $x_{H_2O} = 0.07$, becoming endoergonic above $x_{H_2O} \sim 0.2$, with ΔG reaching 1.47 kcal/mol at $x_{H_2O} = 0.42$ (see Section S5 for details). The combined effect of increasing H₂O concentration and the increasing solvent dielectric constant leads to the equilibrium concentration of the protonated THFDCA that decays as $x_{H_2O}^{-3.647}$, similar to the AA yield decay at $x_{H_2O} > 0.16$ ($\sim x_{H_2O}^{-3.449}$, Figure 5). Since the THFDCA ring-opening rate is expected to be first order in protonated THFDCA, we propose that the large negative reaction order in water for AA production for $x_{H_2O} > 0.20$ is consistent with THFDCA ring-opening becoming the rate-limiting step. In other words, the presence of excess water hinders furan ring-opening because of thermodynamics (due to LeChatelier's principle along with a more subtle change in dielectric constant). The plateau in the AA yield and a near-1st-order reaction rate in H₂ at low H₂O concentrations (Figure 2b and 5) coincide with the change in the sign of the free energy and indicate that ring-opening is not limiting the overall reaction rate at low water fractions.

3.5 Kinetic insights into C-OH bond scission by HI and H₂

Time dependent data from THFDCA in 0.2 M HI at 100 °C reveals one critical ring-opened intermediate (Figure 6a) – 2-(1-oxypropoxy)-hexanedioic acid (PEA), an ester formed between propionic acid and 2-hydroxyhexanedioic acid (HAA, Figure 6b). This species was identified by LCMS, where masses of 217 through 218 amu were observed in the negative scan (Figure S2a). To verify the esterification pathway, experiments were conducted using acetic acid instead of propionic acid, where 2-acetoxyhexanedioic acid (AE) was expected to form. AE was indeed detected by observation of masses of 202 through 203 amu (Figure S2b). The existence of an ester as an intermediate suggests that upon ring opening of THFDCA, esterification of the OH group with the organic acid solvent occurs. The doubly esterification compound, i.e., 2,4-di(1-oxoalkoxy)-hexanedioic acid, was not detected, suggesting that 2,4-dihydroxyhexanedioic acid is not a major intermediate. Thus, the ring opening of THFDCA is unlikely to proceed via the hydrolysis of the protonated THFDCA. In Scheme 4d, we propose that THFDCA ring opening occurs by HI addition across the etheric C-O bond to form an iodine- and hydroxyl-containing species (IHA). In the time-evolved series, however, neither IHA nor other iodine-

containing species is observed, suggesting that these species are easily converted under reaction conditions. IHA likely undergoes facile C-I bond hydrogenolysis to HAA in the presence of HI, H_2 , and the organic acid solvent, and a high concentration of propionic acid as a solvent accelerates esterification. The final hydrogenolysis step to convert HAA/PEA to AA, however, cannot be elucidated from the time-dependent THFDCA data alone.



Figure 6. Time-dependent data of THFDCA ring opening, where only 2-(1-oxopropoxy)-hexanedioic acid (PEA) is observed as an intermediate. Conditions: 1 wt% THFDCA in 0.2 M HI and propionic acid at 100 °C under 500 psi H₂. Solid traces represent the best model fit, taking into account all observed products and one undetected intermediate, 2-hydroxyhexanedioic acid. THFDCA = tetrahydrofuran-2,5-dicarboxylic acid, HAA = 2-hydroxyhexanedioic acid, PEA = 2-(1-oxopropoxy)hexanedioic acid, AA = adipic acid.

Table 2. Reactivity data from malic acid (MA) or fumaric acid (FA) at 160 °C in propionic acid to succinic acid (SA).

Page 25 of 41

	Reactant	C _{HI}	<i>P</i> _{H2} (psi)	Conversion	Y _{SA}	Y _{FA}
1	MA	0.3 M	500	96%	57%	0%
2	MA	0.3 M	0	84%	46%	10%
3	MA	0 M	500	56%	0%	21%
4	FA	0.3 M	500	99%	99%	-
5	FA	0.3 M	0	99%	99%	-
6	FA	0 M	500	10%	0%	-

Conditions: 1 wt% reactant in 15 mL propionic acid with or without HI under 500 psi N₂ or H₂ at 160 °C for 2 h. MA = malic acid, FA = fumaric acid, SA = succinic acid.

To understand the pathway for C-O bond scission in HAA and PEA to yield AA, malic acid (MA) was employed as a model compound, due to its structural similarity to HAA and commercial availability, to probe the interplay between H₂ and HI in removing the hydroxyl/ester group. There are three potential reaction pathways (Scheme 5): (1) dehydration of the C-OH group to fumaric acid (FA), (2) hydrogenolysis of the C-O bond to succinic acid (SA), and (3) esterification of the hydroxyl group to 2-(1-oxopropoxy)-butanedioic acid (PBA). Moreover, FA could undergo hydrogenation to SA (Scheme 5, pathway 4). MA hydrogenolysis at 160 °C in propionic acid (0.3 M HI, 500 psi H₂) occurred with >99% conversion and ~90% selectivity to SA after 2 h of reaction (Table 2, entry 1). When H₂ was replaced with 500 psi N₂ under otherwise identical conditions, MA conversion dropped to 84%, and both SA and FA were observed with yields of 46% and 10%, respectively (Table 2, entry 2). This suggests that in the absence of H₂, several pathways are at play, including proton-mediated dehydration from MA to FA either via protons from HI or propionic acid. The ability of propionic acid to perform dehydration reactions to FA was confirmed by a control experiment where no HI was added to the solution, and 21% yield to FA was observed after using MA as a starting material under 500 psi H₂ (Table 2, entry 3). No



Scheme 5. Possible pathways from malic acid (MA) including (1) dehydration to fumaric acid (FA), (2) hydrogenolysis to succinic acid (SA), and (3) esterification with the solvent to 2-(1-oxopropoxy)-butanedioic acid (BEA).

SA was observed in the absence of HI, suggesting that H_2 cannot participate in the reaction without HI. The formation of SA in the absence of H_2 indicates that HI alone is able to either (1) hydrogenate FA or (2) perform direct hydrogenolysis of MA. To test the first possibility, control experiments were performed using FA as a starting material. After reaction at 160 °C with 0.3 M HI, quantitative yield of SA from FA was seen in both the presence and absence of H_2 (Table 2, entries 4 and 5). FA is unreactive without HI (Table 2, entry 6), providing further evidence of H_2 's inability to directly participate in the reaction without HI. The formation of SA from FA in the presence of HI suggests that HI can indeed facilitate hydrogenation of the C=C bond, via one of two pathways: (1) HI is added across the C=C bond to make 2-iodobutanedioic acid followed by a displacement reaction with HI to form SA and I₂; and (2) HI first decomposes into I₂ and H₂, which is then used to hydrogenate the C=C bond.⁵⁹ In contrast, HI cannot drive the cascade reaction from THFDCA to AA in the absence of H₂. Although H₂ is not required for MA hydrogenolysis, enhanced conversion of MA was observed when HI and external H₂ were co-fed in comparison with that when only HI was employed (see below). This, in combination with the THFDCA conversion in the presence of both HI and H₂, lead to the hypothesis that H₂ participates in the reaction, possibly through HI-mediated activation.



Figure 7. Time dependent data in MA conversion in propionic acid at 500 psi N₂ and 0. 2 M HI (a), in FA conversion in propionic acid at 500 psi H₂ and 0.2 M HI (b), and MA conversion in propionic acid at 500 psi H₂ and 0.2 M HI (c). The dotted line in (c) denotes the use of model A (k_{2A} derived from data in panel a followed by quasi-steady state approximation for C=C hydrogenation), showing a poor fit to the experimental data. Conditions: 1 wt% MA or FA in 15 mL mixture of 0.2 M HI in propionic acid at 100 °C.

Time-resolved MA reduction at 100 °C suggests that direct C-O bond scission occurs only when both H₂ and HI are co-fed. At 100 °C in 0.2 M HI and 500 psi N₂, only dehydration to FA occurs over the course of 6 h, where the majority of MA is converted to 2-(1-oxopropoxy)-butanedioic acid (BEA) via reversible esterification with solvent (Figure 7a). At 160 °C (t = 2 h) under otherwise identical conditions, SA was observed with 46% yield from MA (Table 2). SA was not observed from MA at 100 °C, suggesting that hydrogenation of FA in the presence of HI alone is slow. However, when FA was used as a starting material in the presence of HI and H₂ at 100 °C, FA was quickly converted to SA in the first 1 h of reaction (~99% SA yield, Figure 7b). Thus, the addition of molecular H₂ to HI in propionic acid significantly enhances hydrogenation compared to the case where only N₂ was present. This is further evidenced by time-evolved data when MA was used as a starting material while employing 500 psi H₂ in place of N₂. In this case, FA was not observed as a reaction intermediate (Figure 7c). Instead, SA accumulated at a faster rate than did FA under 500 psi N₂. Below, we use the time-evolved data in Figure 7 to estimate rate constants and provide quantitative assessment of reaction pathways involved in C-OH bond hydrogenolysis.

Kinetic analysis of time-evolved results of MA and FA hydrogenolysis/hydrogenation suggests that direct hydrogenolysis is the dominant mechanism in the removal of C-OH bonds by the combination of HI and H₂, although dehydration and hydrogenation reactions can still occur. As explained above, two mechanisms could explain the conversion of MA to SA: (1) dehydration-hydrogenation and/or (2) direct hydrogenolysis (Scheme 5). To determine relative contributions of the two possible reaction pathways, rate expressions were derived (see Supplementary Information) by incorporating experimentally determined reaction order dependences with respect to all reactants and assuming equilibrium between MA and BEA (Scheme 6). Additionally, the models do not include halogenation/dehalogenation reactions because I-containing species are not observed and are instead lumped into apparent rate constants. Using nonlinear least squares regression (see details in Section 2.4) for MA reduction in the absence of H_2 (Figure 7a), the rate constant for dehydration (k_{2A}) was determined to be 0.052 L mol⁻¹ h⁻¹ with r_{2A} equal to 6.50×10^{-4} mol L⁻¹ h⁻¹, where r_{3A} is 0 because SA formation is too slow without H₂ at 100 °C. In contrast, in the presence of both HI and H2 at 100 °C, FA hydrogenation proceeds too fast to accurately determine a rate constant at different conversions, which is evidenced by the 75% conversion of FA at t =0 h (~10 minute heat-up time, Figure 7b). Thus, in the presence of both HI and H₂, it is reasonable to apply quasi-steady state approximation with FA being a reactive intermediate, i.e., $c_{FA} \sim 0$ and $r_{FA} \sim 0$, when MA is used as a starting material, because $r_{3A} >> r_{2A}$. This is consistent with the time-evolved data from MA in the presence of HI and H₂, where no FA was observed. If the dehydration-hydrogenation pathway is the only mechanism through which MA is converted to SA, employment of k_{2A} as the dehydration rate constant along with the use of a quasi-steady state approximation for FA formation rate should accurately simulate the SA yield over time in the presence of HI and H₂ (Figure 7c). However, doing so results in a poor model fit for SA yield (Figure 7c, dotted lines), suggesting that this model does not provide an accurate description of the reaction network. In light of this, a second model was employed (Model B, Scheme 6), taking into consideration both a dehydration-hydrogenation pathway (k_{2B} and k_{3B}), as well as a direct hydrogenolysis pathway (k_{4B}) . By using the previously determined dehydration rate

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Scheme 6. MA reaction schemes. Model A (a): dehydration from MA to FA and hydrogenation from FA to SA; model B (b): direct hydrogenolysis from MA to SA. MA = malic acid, FA = fumaric acid, SA = succinic acid, BEA = -(1-oxopropoxy)butanedioic acid.

constant ($k_{2A} = k_{2B}$) along with the quasi-steady state approximation for FA, k_{4B} was determined to be 0.25 L³ mol⁻³ h⁻¹ with r_{4B} equal to 1.30×10^{-5} mol L⁻¹ h⁻¹. The rate of direct hydrogenolysis (r_{4B}) is roughly 1.5 times greater than the rate of dehydration (r_{2B}), suggesting the direct hydrogenolysis pathway is the dominant pathway in removing the C-OH bonds in the presence of both HI and H₂, where ~60% of the SA formation rate can be attributed to direct hydrogenolysis. This analysis provides quantitative evidence of H₂'s direct participation in C-O bond scission in the absence of any metal catalyst.

The structural similarity between the C4 model system and ring-opened intermediate from THFDCA suggests that kinetic insights from MA hydrogenolysis could be used to evaluate kinetic parameters from time-resolved data in the ring opening of THFDCA. A two-step THFDCA-to-AA pathway was implemented in the kinetic model: (1) HI-mediated ether bond cleavage and hydrogenation steps to produce HAA from THFDCA (Figure 6b), described by a "lumped" rate constant k_{1C} , and (2) the hydrogenolysis of HAA to AA, described by the rate constant k_{3C} . The equilibrium constant K_{2C} describes the equilibrium between HAA and PEA. Based on the kinetic insights from MA hydrogenolysis, the dehydration/hydrogenation mechanism was not considered. In addition, since no THFDCA conversion was observed when only HI was employed (500 psi N₂), an experimentally determined dehydration rate constant for HAA could not be obtained. By nonlinear least-squares regression, k_{1C} , k_{2C} , K_{2C} , and k_{3C} were evaluated to be 0.80 L³ mol⁻³ h⁻¹, 0.51 L mol⁻¹ h⁻¹, 0.42, and 31 L³ mol⁻³ h⁻¹, respectively. Because $k_{1C} <<$

 k_{3C} , we conclude that the initial ring opening, rather than C-OH bond scission, is rate-determining in AA formation from THFDCA. Interestingly, the rate constant for C-OH bond scission from HAA (k_{3C}) is ~2 orders of magnitude greater when compared to that from MA (k_{3B}). This could stem from the larger separation along the carbon chain between the hydroxyl group and the carboxylic acid group on the opposing end of the molecule, leading to less pronounced electron withdrawing effects.

a Proposed HI/H₂-Mediated Pathway from MA



b Proposed HI/H₂-Mediated Pathway from THFDCA



Scheme 7. Proposed reaction mechanisms. (a) MA: HI-mediated hydrogenolysis pathways with unimolecular displacement or radical-mediated hydrogen activation reactions; (b) THFDCA: HI-mediated ring opening precedes C-I hydrogenolysis steps. MA = malic acid, IBA = 2-iodobutanedioic acid, FA = fumaric acid, SA = succinic acid, THFDCA = tetrahydrofuran-2,5-dicarboxylic acid, IHA = 2-iodo-5-hydroxyhexanedioic acid, HAA = 2-hydroxyadipic acid, PEA = 2-(1-oxopropoxy)hexanedioic acid, IAA = 2-iodohexanedioic acid, AA = adipic acid.

3.6 Redox properties of iodides and hydrogen activation

The activity and kinetic data collected from both THFDCA and MA hydrogenolysis reactions indicate that the combination of HI and H₂ removes C-OH bonds through iodide-mediated H₂ activation. While both H_2 and HI can act as a reducing agent in the hydrogenolysis of MA (Table 2), H_2 is required for AA production (Table 1 and Figure 2a). The presence of HI is necessary to activate H₂, because no hydrogenolysis is observed regardless of reactants. HI is known to decompose into H₂ and I₂ both photochemically⁵⁹ as well as thermochemically.⁶⁰⁻⁶² Moreover, I₂ can be converted to negatively charged, higher order iodide species such as the triiodide (I_3) via the exergonic addition of iodide to iodine $(I_2 + I)$ \rightarrow I₃) in a variety of solvents.⁶³⁻⁶⁵ Such reactions of I⁻ demonstrate its ability to act as reducing agent through either direct electron transfer or the production of H₂, e.g., R-OH + 2 HI \rightarrow R-H + H₂O + I₂ (Scheme 7a, bottom pathway).^{66, 67} Degradation of iodide was observed in our system by analyzing postreaction solutions by ultraviolet-visible spectroscopy (UV-Vis), which show strong absorption bands at \sim 350 nm and 290 nm (Figure S3a). These bands have been assigned to the excitation of an electron from the π and σ molecular orbitals of triiodide, respectively, to the σ^* orbital in triiodide.^{68, 69} Furthermore, the intensity of these bands increases over the course of reaction (4 h), which reflects the gradual conversion of iodide and the formation of triiodide (Figure S3b). Similar level of conversion of I⁻ was also observed in the absence of THFDCA, indicating that the ring opening of THFDCA is unrelated to the degradation of HI. The first step in the activation of the C-OH bond in MA is likely initiated by iodide substitution, thereby forming 2-iodobutanedioic acid (IBA, Scheme 7a), which is consistent with mechanisms proposed elsewhere.⁷⁰ However, this species is not observed by liquid chromatography after reaction, which could be due to the rapid removal of C-I bonds in the subsequent hydrogenolysis step, which is proposed to proceed via a displacement reaction from HI, forming C-H and I₂ in the absence of molecular hydrogen.^{66, 67, 70, 71}We propose that molecular hydrogen is activated via the formation of an iodine radical species upon the activation of the C-I bond, which produces C-H and HI. This is consistent with the enhanced SA rate in the presence of molecular hydrogen (Figure 7), as well as a first order dependence on molecular H_2 (Figure 2a). Butylated hydroxytoluene (BHT), a radical scavenger, was introduced to the

reaction system to test the hypothesis of the involvement of radical species in the reaction. However, the hydroxyl group in BHT is not stable under reaction conditions, and thus no unequivocal conclusion can be drawn. The ability of HI to convert MA to SA without H_2 , as well as the structural similarity between HAA and MA, suggest that HI alone should be able to mediate the hydrogenolysis of HAA to AA. However, no AA is produced from THFDCA in the absence of molecular hydrogen (Table 1), which indicates that H₂ directly participates in the ring opening of THFDCA. Another possible mechanism for hydrogen activation is by reacting H₂ with I₂ and/or I₃⁻ to reform HI, because I₂ and I₃⁻ are produced in the spontaneous degradation of HI. Thermodynamically, the conversion of HI into H₂ and I₂ is reversible,⁶⁰⁻⁶² where $\Delta G_{f,HI}^0 \sim 1.3$ kJ/mol at 25 °C. Using the Van't Hoff equation and thermodynamic relationships, this value decreases to a value between -7.1 and -10 kJ/mol in the temperature range relevant to this study (100 - 160 °C). Thus, it is plausible that H_2 participates in the reaction by regenerating HI through its reaction with I_2 or I_3^- . This possibility was tested by co-feeding molecular I_2 or I_3^- (0.3 M) with THFDCA and molecular H₂ (500 psi) in propionic acid at 160 °C. However, after 2 h of reaction, no AA was observed, suggesting that I_2 and I_3^- cannot activate H_2 . While the exact pathway through which H_2 is activated with the assistance of Γ remains unclear, we propose a plausible mechanism based on experimental and computational results in the following section.

3.7. Proposed reaction mechanism from THFDCA to AA based on activity studies and kinetic measurements

Combining data from sections 3.2 through 3.6, we propose that the AA formation from THFDCA proceeds by HI-mediated ring opening followed by C-I/C-OH hydrogenolysis steps in the presence of HI and H₂ (Scheme 7b). In section 3.2, we propose that the initial ring opening proceeds by HI-mediated ether cleavage, where HI provides both a proton to form an oxonium intermediate and an iodide ion to attack the α -carbon, thereby cleaving the C-O bond to form IHA. When both HI and H₂ are present, hydrogenolysis of IHA's C-I bond to HAA is inferred by a structurally similar model compound (MA) in section 3.5. There are two possible causes for the absence of HAA as an intermediate: (1) fast and

ACS Catalysis

reversible esterification to PEA with propionic acid (the solvent), and (2) fast iodide substitution to 2iodohexanedioic acid (IAA) and the subsequent hydrogenolysis to AA. This proposed mechanism is supported by both activity data (Tables 1 and 2) and kinetic measurements presented in sections 3.1 through 3.6, as discussed in detail below.

Hydrogenolysis of the C-I bond in IHA is likely the rate-determining step in AA formation, although the conversion of a C-I bond to a C-H bond is unlikely to be a single elementary step given the high number of reactant moleculse involved in this step. Although the time-dependent iodine/triiodide evolution from HI provides evidence of iodide's reducing ability, e.g., 2 HI \rightarrow H₂ + I₂, iodide alone in the absence of H₂ is incapable of driving the ring opening of THFDCA (Table 1). We hypothesize that THFDCA is related to IHA via two sequential equilibria, i.e., protonation of THFCDA to form the corresponding oxonium, and I mediated ring opening of the oxonium intermediate to form IHA. Fitted rate constants suggest that the hydrogenolysis of the C-I bond in IHA is the rate determining step in the presence of hydrogen (k_{1C} (~ 0.8 L³ mol⁻³ h⁻¹) << k_{3C} (~31 L³ mol⁻³ h⁻¹)), where the incorporation of molecular H₂ could occur as a single, concerted step or by heterolytic H-H bond dissociation to form C-H and H-I as a result. Either mechanism is consistent with the observed first order dependence in molecular H₂, although the exact C-I hydrogenolysis and H₂ activation mechanism cannot be determined based on the experimental or theoretical evidence in this work. The absence of HAA in the time-evolved kinetic experiments provides further consistency with C-I bond scission being the rate-determining step (Figure 6a, yellow trace/markers). In other words, once the first hydrogenolysis step occurs to form HAA, its conversion to AA is very fast such that its accumulation in the reactor is negligible. In addition to AA, PEA was also observed in time resolved experiments, indicating that it is a side product, rather than a direct intermediate in AA formation. The accumulation of PEA is attributed to relatively high rate constant ($k_{2C} \sim 9.0 \text{ L} \text{ mol}^{-1} \text{ h}^{-1}$) for the esterification reaction as well as the high concentration of propanoic acid (solvent). The observation of PEA provides strong evidence for the presence of HAA as a reactive intermediate.

Experimentally determined reaction orders of THFDCA, HI, and H_2 are also consistent with the hypothesis that the formation of HAA via hydrogenolysis of the C-I bond is the rate-limiting step in the AA formation. The overall rate expression based on the proposed mechanism is:

$$r_{\rm rds} = r_{\rm AA} = k_{\rm 1C} C_{\rm THFDCA} C_{\rm HI}^2 C_{\rm H_2}$$

where k_{1C} includes the equilibrium constants for protonation, iodide addition/ether bond scission, and C-I bond scission steps. The first-order dependence of the overall rate on THFDCA concentration agrees well with the measured reaction order for THFDCA (0.9). This is because the concentration of THFDCA is related to that of IHA, a reactant in the rate-limiting step, via two equilibria. HI plays a multi-faceted role in cleaving the C-O bond through equilibrated ether cleavage steps, by acting as both a proton (H⁺) and a nucleophile (I) to form IHA. This leads to a first-order dependence of the overall rate on the concentration of both proton and iodide, and thus a second order dependence on the concentration of HI. This is consistent with the measured reaction order of 1.6 for HI. The observed first-order kinetics with respect to molecular hydrogen (~0.9) is also consistent with the direct involvement of H₂ in the proposed rate-limiting step. The use of isotopic labeling could lead to more detailed insights into the hydrogenolysis mechanism; however, the multiple sources of proton in the reaction system, i.e., organic acids, HI and water, are likely to incur significant H/D scrambling in the reaction mixture, making analysis of such experiments inconclusive.

In Figure 8, we report the first-principles reaction energy diagram for the THFDCA-to-AA conversion via the ring-opening/C-I hydrogenolysis mechanism. Reaction energies range from -0.78 kcal/mol (IAA and IHA reduction by H_2) to +1.36 kcal/mol (ring-opening in the protonated THFDCA), making the reaction mechanism thermodynamically feasible at experimental reaction conditions. As the IAA reduction being the rate-limiting step implies equilibrium between THFDCA, protonated THFDCA, and IAA, and IAA lies 0.32 kcal/mol higher in energy than THFDCA, in absence of H_2 the equilibrium will be shifted towards THFDCA, which is consistent with negligible THFDCA conversion in the experiment.





Figure 8. First-principles energy diagram for THFDCA conversion process to AA. For reaction steps 3-5, solvation energies of all species except H_3O^+ were calculated using the CPCM implicit solvent model; the H_3O^+ solvation energy was estimated to be -114.06 kcal/mol, as described in the text. Energy of reaction step 1 was estimated using CPCM for all species (see the text). Reaction barriers are not reported. Gibbs free energies are reported at 25 °C.

The current study suggests that HI acts analogously to a bifunctional catalyst that possesses strong Brønsted acidity and the ability to activate hydrogen, which can cleave ether bonds and C-OH bonds very selectively without attacking the higher order oxygenated functional groups, i.e., carboxylic acids. Similar observations were made elsewhere, where carbonyl groups in HMF could not be reduced by HI while C-OH groups could.⁷⁰ It has been reported that reduction of terminal carboxylic acid groups is prevalent over selective ring opening catalysts such as silica-supported metal/metal oxides which were employed by Tomishige et al. to produce 1,5-pentanediol from tetrahydrofuryl alcohol.⁷²⁻⁷⁵ These catalysts, e.g., Rh-ReO_x/SiO₂, are able to activate C-O bonds in cyclic ethers, albeit through different proposed mechanisms and can lead to (over)hydrogenation of the carboxylic acid groups.⁷⁶ In the mechanism proposed by Tomishige et al., high selectivity toward α,ω -diols from hydroxymethyltetrahydrofurans stems from selective adsorption of the hydroxymethyl side group onto ReO_x sites, where Rh-bound hydride species can selectively break the C-O bond leading to the final

product. A key difference in our system, however, lie in (1) direct activation of the ether bond by strongly acidic protons, and (2) indirect C-O bond cleavage step by iodide substitution prior to hydrogen addition. Indirect C-O bond cleavage by iodide addition and C-I bond hydrogenolysis could rationalize the inability of the HI-based system in reducing the carboxylic acid group.^{76, 77} Another feature of the current system is the cooperative employment of an organic acid solvent, while more typical solvents such as water or alcohols work poorly in producing AA with the combination of H_2 and HI. Organic acid solvents likely play a role in tuning the acid/base properties of the system, facilitating the protonation of the substrate (THFDCA) to its oxonium ion which speeds up the reaction rate to AA considerably. Water, instead of an organic acid, acts as the strongest base in the system, thereby retarding the rate of protonation of the substrate and, subsequently, ring opening to AA. We have furthermore rigorously demonstrated that H₂ plays an active role in reducing MA, FA, and THFDCA to their corresponding alkylated diacids. When HI is used alongside molecular H₂, enhanced activity, both in THFDCA hydrogenolysis and in MA hydronolysis, is observed, which provides strong evidence that H_2 participates directly in the reaction. Thus, the HI/H₂-mediated hydrogenolysis mechanism provides an approach for selective ring opening of carboxylic acid-containing furanic compounds without the need for expensive noble metals.

4. Conclusions

In summary, H_2 and HI in organic acid solvent are capable of effectively forming AA from biomass-derived THFDCA without any metal catalyst. HI exhbits a $\sim 2^{nd}$ order relationship, while THFDCA and H_2 are closer to $\sim 1^{st}$ order. Organic acid solvents, e.g., acetic and propanoic acids, promote the ring opening reaction while water suppresses the reactivity. Calculations indicate that in an organic acid solvent containing small water fractions, THFDCA acts as a stronger base than H_2O , which allows for effective protonation of THFDCA, facilitating the ring opening and the subsequent hydrogenolysis. When the water content is high, it becomes a stronger base and inhibits THFDCA's protonation. Time-

dependent data with both THFDCA and MA reveal key intermediate species, which contain esters produced from solvent-mediated esterification reactions with hydroxylated intermediates. Kinetic modeling reveals that the direct hydrogenolysis mechanism is dominant, although a dehydration/hydrogenation pathway could still occur. Based on these results, we propose an overall reaction mechanism. In the first part of the mechanism, HI cleaves the C-O bond by an S_N2-type substitution reaction whereby the THFDCA molecule is first protonated, and an iodide is added to the α carbon. Once the ring is opened, H₂ can be added to the molecule via iodide-mediated H₂ activation. The insights described herein grant insights into the development of solid catalysts that maintain strong acidity and mild hydrogenation ability.

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Associated Content

Supporting Information Available: Kinetic model derivations, thermodynamic calculations, pK_a predictions in organic acid solvent, reaction order analysis methodology, liquid chromatographymass spectrometry data, iodide evolution data.

This material is available free of charge via the Internet at http://pubs.acs.org.

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Page 39 of 41

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