ORGANIC CHEMISTRY

Reaction of H_2 with mitochondria-relevant metabolites using a multifunctional molecular catalyst

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The Krebs cycle is the fuel/energy source for cellular activity and therefore of paramount importance for oxygen-based life. The cycle occurs in the mitochondrial matrix, where it produces and transfers electrons to generate energy-rich NADH and $FADH_2$, as well as C_4-, C_5-, and C_6-polycarboxylic acids as energy-poor metabolites. These metabolites are biorenewable resources that represent potential sustainable carbon feedstocks, provided that carbon-hydrogen bonds are restored to these molecules. In the present study, these polycarboxylic acids and other mitochondria-relevant metabolites underwent dehydration (alcohol-to-olefin and/or dehydrative cyclization) and reduction (hydrogenation and hydrogenolysis) to diols or triols upon reaction with H_2, catalyzed by sterically confined iridium–bipyridyl complexes. The investigation of these single–metal site catalysts provides valuable molecular insights into the development of molecular technologies for the reduction and dehydration of highly functionalized carbon resources.

INTRODUCTION

The recent depletion of fossil fuel resources has impelled industrial and academic researchers to search for alternative carbon-based energy sources. Considerable effort has been invested in biotechnology and sustainable/green technologies to develop a chemical industry in which renewable energy resources complement dwindling fossil fuel sources for the new millennium. A round-table discussion of the U.S. Department of Energy identified the top 30 value-added chemicals derived from biomass, which included various (poly)carboxylic acids and polyols (*1*). These chemicals exist in high oxidation and/or highly oxygenated states, and thus, current state-of-the-art oxidation catalysts must be substantially modified to achieve the reduction and dehydration of these biorenewable resources (*2*, *3*).

The top 30 value-added chemicals reevaluated were further narrowed to a top 12 list, in which the highest value-added carboxylic acid (CA) is succinic acid (*4*, *5*). Succinic acid has been produced in conventional petrochemical or coal industry, mainly from acetylene, butane, or 1,4-butadiene, and hydrogenated to 1,4-butanediol (1,4-BDO) using heterogeneous catalysts (*5*). In particular, the eight–hydrogen atom (or 8*e*)–reduced, doubly dehydrated form of succinic acid, 1,4-BDO, is a highly versatile synthetic intermediate. 1,4-BDO is an important commodity chemical used to manufacture over 2.5 million tons of valuable polymers per year, including poly(butylene) terephthalate and poly(urethane)s (*6*). Yet, reports dealing with the selective reduction of succinic acid to 1,4-BDO using molecular catalysis are still limited (*5*, *7*–*9*), particularly those reporting systematic trial-and-error investigations. Various patents and scientific articles on the topic of heterogeneous catalysts for the hydrogenation of succinic acid have reported that numerous reaction parameters influence the product distribution (*5*, *10*); thus, the development of more sophisticated catalysts is required to control the product yields.

In addition to succinic acid, substantial attention should be paid to the reduction and dehydration of more highly functionalized C_4-, C_5-, and C_6-polycarboxylic acids [PCAs, including dicarboxylic acids (DCAs) and tricarboxylic acids (TCAs)], such as fumaric acid (*11*), malic acid (*12*), oxaloacetic acid (*13*), 2-oxoglutaric acid (*14*), aconitic acid (*15*), and citric acid (*16*), which are potential carbon feedstocks produced as metabolites in the Krebs cycle (*17*) [also known as the TCA cycle or citric acid cycle; Figs. 1A and 2A], which operates in the mitochondrial matrix in the cells of most plants, animals, fungi, and many bacteria. Further biotechnological modification of this energy-yielding metabolic pathway could enable the scalable production of C_4-, C_5-, and C_6-PCAs, which can be expected to be upgraded subsequently using catalysts that effectively reduce and dehydrate these compounds (the goal of this research). The Krebs cycle is mainly controlled by oxidation and hydration (with decarboxylation) reactions of various enzymes. The hydrogen (electron)–trapping cofactors nicotinamide adenine dinucleotide and flavin adenine dinucleotide–positive are involved in controlling the product distribution across different C_4-, C_5-, and C_6-PCAs. If an artificial catalyst was able to reverse the natural Krebs cycle (written formally in a clockwise fashion in Fig. 1A) by promoting the usually unfavorable reduction (hydrogenation) and dehydration [hydrogenolysis/hydrodeoxygenation (HDO)] (*18*, *19*), which are reactions in an anticlockwise fashion, then diverse functionalized C_4-, C_5-, and C_6-metabolites could be transformed into a family of energy-rich polyols without recruiting natural enzymes. In this context, the development of previously unidentified, robust, and unidirectional catalysts, i.e., catalysts that promote hydrogenations and dehydrations while they suppress the reverse processes, represents a great challenge since the highly oxygenated or nitrogenated substrates abundant in nature can easily poison catalytically active sites via substrate/product inhibition, and the reverse dehydrogenation reaction sometimes occurs, particularly at high temperature. Unfortunately, however, systematic studies to establish a molecular rationale and molecularly predictable approaches to obtain high productivity and selectivity in divergent reduction/dehydration reactions of PCAs all the way to different polyol products remain elusive.

As part of our ongoing interest in developing new molecular technologies for the catalytic reduction and/or dehydration of organic compounds in high oxidation states (*20*), peptides and plastics (*21*, *22*), and monocarboxylic acids (MCA) including fatty acids and α-amino acids (*23*–*26*), bioalcohols (*27*), and CO_2 (*28*), we introduce here the

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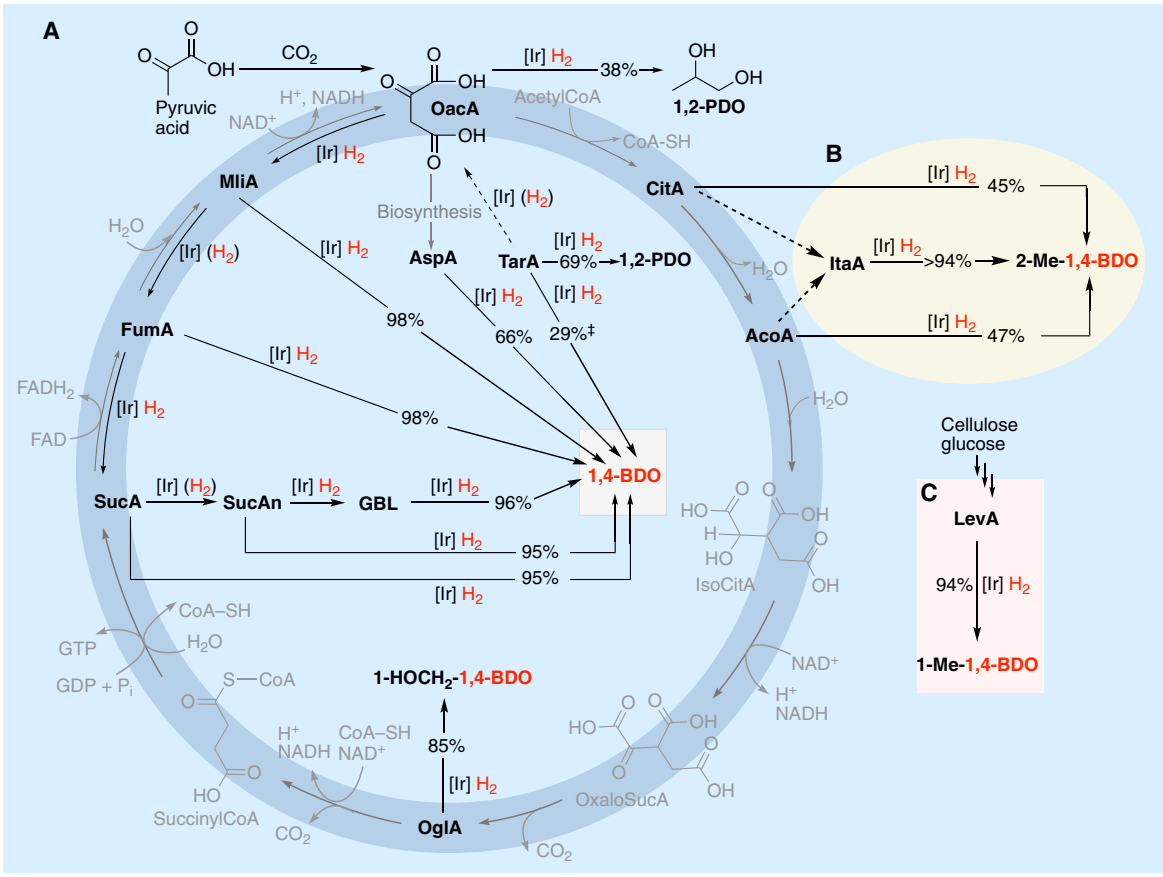


Fig. 1. Redrawing the map for the chemical transformation of Krebs cycle–relevant metabolites. (**A**) Single–[Ir] site–catalyzed hydrogenation and dehydration reactions in this work (black arrows and red text) and the original Krebs cycle (blue ring and gray text/arrows). Dashed arrows are proposed partial pathways in the hydrogenation of each substrate with Ir-**a**. ‡1,2-Propanediol (1,2-PDO; 36%) was also obtained. (**B**) Hydrogenation of cytoplasm metabolites (pale green ellipse). (**C**) Hydrogenation of the sugar-derived artificial feedstock LevA. For definitions of abbreviations and acronyms, see Fig. 2A. Isocitric acid (IsoCitA), oxalosuccinic acid (oxaloSucA), and succinyl-coenzyme A (succinylCoA) are rarely available.

coordinatively saturated phosphine–bipyridine–phosphine (PNNP) iridium (Ir) complex Ir-**a** (Fig. 2). Ir-**a** is a novel, versatile, and robust precatalyst whose multifunctional, sterically confined Ir–bipyridyl (bpy) framework can promote various dehydration and hydrogenation processes in a one-pot fashion; the apparent cleavage of C—O and C—N σ bonds under concomitant decarboxylation to induce HDO and even hydrodeamination (HDA) reactions is followed by the hydrogenation of various C═C and C═O bonds of ketones, acid anhydrides, and esters, which affords C_3, C_4, and C_5 polyols (Fig. 2A). The catalytic framework generated upon addition of n H_2 (n = 1 to 6) to Ir-**a** maintains its structural robustness, with no detachment of the ligand from the Ir center or C—P bond cleavage (*21*). Thus, the complex retains good catalytic activity even under strenuous conditions [hydrogen pressure (P_{H2}) = 4 to 8 MPa; reaction temperature (T) = 140° to 200°C; reaction time (t): 18 to 120 hours]. The single catalytically active site of this bespoke Ir–bpy framework is sterically protected by four cyclohexyl (Cy) groups; the small size of the active pocket favors the selective uptake, coordination, and activation of H_2 (Fig. 2B, left). The confined environment of the single metal site also protects the catalyst from deactivation via bidentate coordination by the relatively large functional groups of the highly oxygenated and nitrogenated compounds and even from monodentate coordination to the virtually coordinatively saturated Ir center.

RESULTS AND DISCUSSION

Reaction of H_2 with C_4-DCAs and their anhydrides

We have recently reported that the (PNNP)ruthenium (Ru) complex Ru-**a** (Fig. 2B, right) serves as a molecular precatalyst for the hydrogenation of unactivated amides, including polymer nylons (*21*). However, Ru-**a** [1 mole percent (mol %)] was ineffective for the hydrogenation of succinic acid to 1,4-BDO (Fig. 3A, entry 1) under the reaction conditions used for amide hydrogenation [NaH (10 mol %); P_{H2} = 6 MPa; T = 180°C], and only γ-butyrolactone (GBL) was produced in 21% yield. We then screened different metal centers with different tetradentate PNNP ligands in the presence of a catalytic amount of NaH (6 mol %) for the hydrogenation of succinic acid and found that Ir-**a** (1 mol %) was the most effective to furnish 1,4-BDO in 95% yield. The state-of-the-art Ir-complex Ir-**d** [Crabtree complex; (*29*)] was also tested (Fig. 3A, entry 5), albeit it showed, similar to the water-soluble Vaska complex, merely scant activity, producing only GBL (*5*).

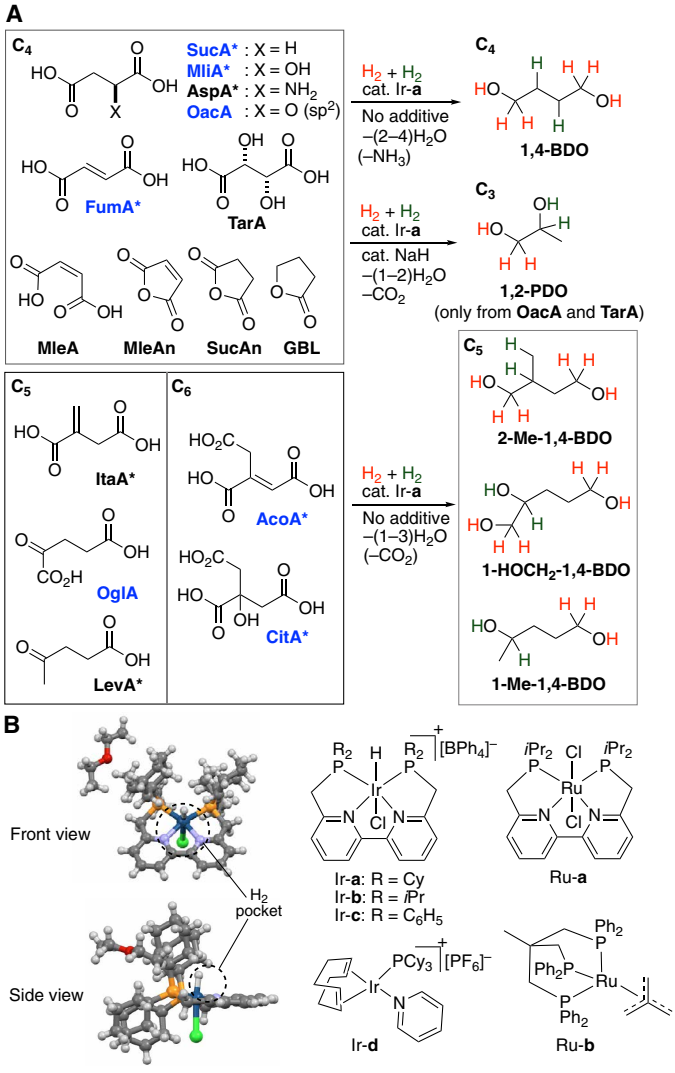
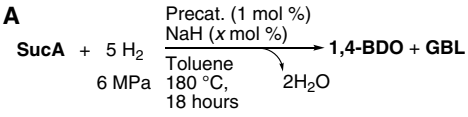


Fig. 2. Summary of this work. (**A**) Renewable carbon feedstocks that afford various 1,4-BDO derivatives and 1,2-propanediol. Compound names in blue are Krebs cycle metabolites, while those marked with asterisks are possible feedstocks listed as top 30 value-added chemicals in the initial U.S. Department of Energy/the National Renewable Energy Laboratory report in 2004 (*1*). Succinic acid (SucA), malic acid (MliA), aspartic acid (AspA), oxaloacetic acid (OacA), tartaric acid (TarA), fumaric acid (FumA), maleic acid (MleA), maleic anhydride (MleAn), succinic anhydride (SucAn), γ-butyrolactone (GBL), itaconic acid (ItaA), 2-oxoglutaric acid (OgIA), levulinic acid (LevA), aconitic acid (AcoA), and citric acid (CitA). (**B**) Single-crystal x-ray diffraction structure of Ir-**a** (left; Et_2O included). Color key: Ir (blue), N (purple), P (orange), Cl (green), O (red), and H (white). See also fig. S1. $[BPh_4]^-$ is omitted for clarity. Ir and Ru complexes for hydrogenation tested in this work (right).

The intended role of NaH was to remove a methylene (CH_2PCy_2) hydrogen atom from Ir-**a** to promote the dearomatization of a bpy fragment (*21*, *22*, *30*–*33*). This step may be followed by the full hydrogenation of the bpy framework under strenuous conditions; Ru-**a** undergoes such deprotonation and hydrogenation in the presence of NaH (*21*, *22*). However, after numerous control experiments for the hydrogenation of succinic acid with Ir-**a** (1.5 mol %), we found that a comparable hydrogenation of succinic acid occurs even without NaH, which generates 1,4-BDO in 86 ± 8% yield (average of six runs; Fig. 3B, entry 1 and table S1, entry 6). A mercury test revealed that the reduction of succinic acid occurred by homogeneous catalysis, as there was no significant difference in the amount of 1,4-BDO in the presence of Hg (0.22 M; table S1, entry 10). Ir-**a** derivatives Ir-**b** and Ir-**c**, which bear similar PNNP ligands with different steric demands, showed comparable or lower catalytic activity (Fig. 3B, entries 2 and 3). The groups of Leitner and Klankermayer as well as that of Frediani have previously reported that Ru-Triphos [$(Ph_2PCH_2)_3CMe$] catalyzes the hydrogenation of succinic acid under harsh conditions (*7*, *8*). Therefore, we retested Ru-Triphos complex Ru-**b** in both the presence and absence of NaH (Fig. 3A, entries 2 and 3) and found that its catalytic activity (1,4-BDO: 83 to 90%; three independent runs) was comparable to that of Ir-**a**. Both the P_{H2} and T values are critical for the production of the desired product 1,4-BDO; GBL was formed exclusively in good to moderate yield at lower temperatures (79%) or at lower P_{H2} (58%; table S2). GBL was hydrogenated almost quantitatively to 1,4-BDO by Ir-**a** within 4 hours at 180°C or within 18 hours at 160°C (Fig. 3B, entry 13 and table S3). Capitalizing on the versatility of Ir-**a**, the dehydrogenated forms of succinic acid, i.e., fumaric acid and its *Z*-isomer maleic acid, were also hydrogenated smoothly to give 1,4-BDO in near-quantitative yield (Fig. 3B, entries 4 and 5). The anhydrides of succinic acid and maleic acid were also hydrogenated to exclusively produce 1,4-BDO (Fig. 3B, entries 11 and 12), although the hydrogenation of maleic anhydride was somewhat sluggish (t = 18 hours: 35%; t = 66 hours: 91%). All control experiments suggest that the hydrogenation of fumaric acid to 1,4-BDO follows the pathway fumaric acid→succinic acid→succinic anhydride→GBL→1,4-BDO.

We then determined the time-conversion profile during the Ir-**a** (1.5 mol %)–promoted hydrogenation of fumaric acid (P_{H2} = 6 MPa; T = 180°C; t = 0 to 18 hours) and plotted the changes in the product distribution as a function of time (Fig. 3C and tables S4 and S5). Fumaric acid was rapidly hydrogenated to succinic acid (2*e* reduction: t < 1 hour), which was consistently detected over the first 12 hours of reaction. The conversion of succinic acid to GBL was slow (t = 10 to 12 hours), while the concentration of succinic anhydride was negligible until t = 18 hours, which suggests that succinic anhydride, once formed, was rapidly hydrogenated to GBL (4*e* reduction), even in the presence of succinic acid, which provided slightly acidic conditions. The subsequent hydrogenation of GBL to 1,4-BDO (4*e* reduction) did not begin until succinic acid had completely disappeared (t = ~14 hours). Upon complete consumption of succinic acid, the hydrogenation of GBL commenced suddenly and was completed within 2 hours. It can thus be concluded that the catalyst for the hydrogenation of succinic anhydride is alive but that for GBL is not generated or resting in an inactive form, under acidic conditions provided by the inherent acidity of succinic acid. Unlike significant effects of a base additive observed on ester/lactone hydrogenation by a Ru- or cobalt-pincer complex (*32*, *33*), base is not necessarily needed for the hydrogenation in the present system. During the overall reaction to produce 1,4-BDO from fumaric acid (fumaric acid→succinic acid→succinic anhydride→GBL→1,4-BDO), the slowest reaction step was the dehydrative cyclization of succinic acid to succinic anhydride, which required ca. 12 hours. A similar time profile of the product distribution was observed under the relatively basic conditions provided by the combined use of Ir-**a** and NaH (1.5:9 mol %; fig. S2), except that the complete conversion of succinic acid to succinic anhydride was faster [ca. 10 hours versus 14 hours without NaH (vide supra)], and the hydrogenation of GBL to 1,4-BDO was slower [ca. 6 hours versus 2 hours without NaH (vide supra)].

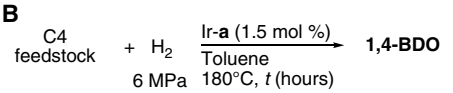
A



Entry	Precat.	NaH *x* (mol %)	1,4-BDO yield (%)[b]	GBL yield (%)[b]
1[b,d]	Ru-**a**	10	nd[c]	21
2	Ru-**b**	6	75	3
3	Ru-**b**	0	90	3
4	Ir-**a**	6	95	5
5[b,d]	Ir-**d**	6	nd[c]	19

[a]Unless otherwise specified, the reactions were carried out using precat.:SucA:NaH = 1:100:0–10 mol % in toluene for 18 hours, starting with P_{H2} = 6 MPa at 25°C. [b]Of ^{1}H NMR (DMSO-d_6) based on internal standard. [c]Not detected by ^{1}H NMR. [d]Determined by GC (table S15).

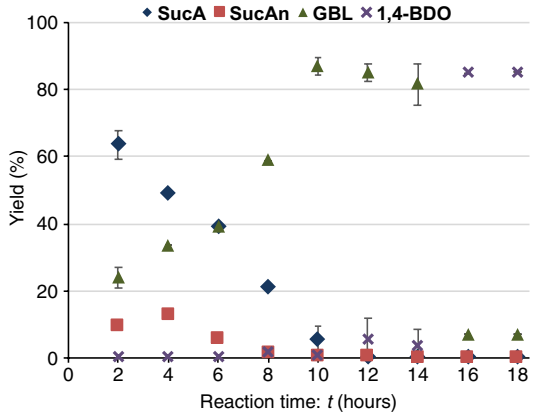
B



Entry	C4 feedstock	*t* (hours)	1,4-BDO yield (%)[b]	GBL yield (%)[b]
1	**SucA**	18, 42	86±8[h], 91	5±2[h], 2
2[c]	**SucA**	18	44	41
3[d]	**SucA**	18	81	2
4	**FumA**	18, 42	81, 98	3, 2
5	**MleA**	18, 42	80, 97	16, 3
6	**MliA**	42	98	2
7[e]	**AspA**	66	66	4
8	**TarA**	90	29(36)[g]	–[i]
9[f]	**TarA**	90	14(69)[g]	–[i]
10[f]	**OacA**	24	~1(38)[g]	–[i]
11	**MleAn**	18, 42, 66	35, 88, 91	28, 2, 3
12	**SucAn**	4, 8	7, 95	62, 2
13	**GBL**	4	96	–[i]

[a]Unless otherwise specified, the reactions were carried out using Ir-**a**:feedstock = 1.5:100 mol % in toluene, starting with P_{H2} = 6 MPa at 25 °C. [b]Of ^{1}H NMR (DMSO-d_6), based on internal standard. [c]Ir-**b**. [d]Ir-**c**. [e]2-Pyrrolidone (12%) by-produced. [f]NaH (9 mol %) was used. [g]Of yield of 1,2-PDO. [h]Average of 6 runs. [i]Not detected.

C



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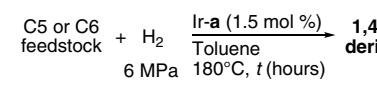

Entry	C5 or C6 feedstock	*t* (hours)	Main product	1,4-BDO deriv. yield (%)[b]	GBL deriv. yield (%)[b]
1	**OglA**	72	**1-HOCH$_2$-1,4-BDO**	85(78)[c]	nd[d]
2	**AcoA**	120	**2-Me-1,4-BDO**	47(42)[c]	nd[d]
3	**CitA**	120	**2-Me-1,4-BDO**	45(32)[c]	nd[d]
4[e]	**ItaA**	72	**2-Me-1,4-BDO**	>94	<6[f]
5	**LevA**	18	**1-Me-1,4-BDO**	94	6

[a]Unless otherwise specified, the reactions were carried out using Ir-**a**:feedstock = 1.5:100 mol % in toluene, starting with P_{H2} = 6 MPa at 25 °C. [b]Of ^{1}H NMR (DMSO-d_6), based on internal standard. [c]Of isolated, purified prodcut. [d]Not determined. [e]1,4-dioxane instead of toluene. [f]2-Me- (<2%) and 3-Me-GBL (<2%).

E

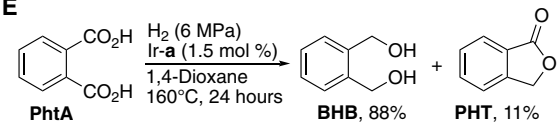

Fig. 3. Experimental results: Hydrogenation of various C_4-, C_5-, and C_6-PCA feedstocks and phthalic acid using Ir-a and other metal complexes. (**A**) Hydrogenation of SucA with different Ir and Ru complexes. DMSO, dimethyl sulfoxide; NMR, nuclear magnetic resonance; GC, gas chromatography. (**B**) Hydrogenation of C_4-feedstocks with Ir-**a**, Ir-**b**, and Ir-**c**. (**C**) Time conversion (yield) plots of the hydrogenation of FumA with Ir-**a** (1.5 mol %) without NaH. (**D**) Hydrogenation of C_5 and C_6 feedstocks with Ir-**a**. (**E**) Hydrogenation of phthalic acid (PhtA) with Ir-**a**.

Reaction of H_2 with more functionalized C_4-DCAs

Subsequently, we investigated the hydrogenation of malic acid, aspartic acid, and tartaric acid, i.e., functionalized C_4-DCAs. Malic acid is a Krebs cycle metabolite (*12*, *17*); aspartic acid is biosynthesized by the transamination of oxaloacetic acid (Krebs cycle metabolite) via enzymatic processes involving aspartase (*34*). Tartalic acid can be produced from vitamin C (L-ascorbic acid; or from 5-oxo-D-gluconic acid) by scalable fermentation (*35*). Since Ru-**b** showed catalytic activity similar to that of Ir-**a** for the hydrogenation of succinic acid (vide supra), the hydrogenation of these C_4-DCAs using catalytic amounts of Ru-**b** was examined (P_{H2} = 6 MPa; T = 180°C, t = 18 to 90 hours; table S6). Malic acid was hydrogenated to 1,4-BDO; the yield was found to be the same (70 ± 1%) at t = 18 and 42 hours. This result suggests that the Ru-**b**–derived catalyst is relatively vulnerable and deactivated within 18 hours, while the Ir-**a**–derived catalyst continues to show good activity thereafter (1,4-BDO: 63% for t = 18 hours; 98% for t = 42 hours). When aspartic acid and tartaric acid were hydrogenated using Ru-**b**, the yield of 1,4-BDO was marginal in both cases (~4%), probably because of substrate inhibition of the catalyst. In sharp contrast, the Ir-**a**–derived catalyst is more robust and maintains its activity during the hydrogenation of malic acid, aspartic acid, and tartaric acid to furnish 1,4-BDO in 98, 66, and 29% yield, respectively (Fig. 3B, entries 6 to 8, and tables S7 and S8; see also proposed multistep HDO/HDA and hydrogenation sequences: figs. S3 to S5). In contrast, 1,2-propandiol (36%) is the main product formed from tartaric acid. When NaH (9 mol %) was used for the preactivation of Ir-**a**, 1,2-propanediol and 1,4-BDO were produced in higher (69%) and lower yield (14%), respectively (Fig. 3B, entry 9). Thus, the complex reaction pathway for the formation of 1,2-propanediol with 1,4-BDO as a side product may involve the dehydration of tartaric acid to oxaloacetic acid as a common process, followed by two distinct multistep sequences to generate either 1,2-propanediol or 1,4-BDO (fig. S5). When the potential intermediate oxaloacetic acid, which is the starting compound in the Krebs cycle, was hydrogenated, 1,2-propanediol (38%) was detected, while the formation of 1,4-BDO was negligible (~1%; Fig. 3B,

entry 10, and tables S9 and S10). The decarboxylation of oxaloacetic acid that leads to pyruvic acid was much faster than the hydrogenation of the ketone. The sequence of dehydration and decarboxylation of tartaric acid giving pyruvic acid was promoted previously by a substoichiometric amount of $KHSO_4$ at 210° to 220°C (*36*). The long-lived catalytic activity of Ir-**a** in the hydrogenation of the three C_4-DCAs is probably due to the almost exhaustive coordinative saturation and steric confinement of the Ir center, which provide structural robustness to the Ir-**a**–derived catalyst. These electronic and steric features prevent substrate/product inhibition of the catalyst, namely, deactivation of the catalyst by the highly functionalized substrates malic acid, aspartic acid, and tartaric acid, which are probably able to more tightly ligate the coordinatively less saturated Ru center of Ru-**b** through bidentate chelation.

Reaction of H_2 with C_5- and C_6-PCA

2-Oxoglutaric acid and itaconic acid are C_5-DCAs; the former is a Krebs cycle metabolite (*14*, *17*), while the latter can be fermentatively biosynthesized in the cytoplasm through the *cis*-aconitic acid–decarboxylase-catalyzed decarboxylation of *cis*-aconitic acid (a C_6 acid involved in the Krebs cycle), which is released from the mitochondria (*37*). Both DCAs undergo hydrogenation using H_2 and Ir-**a**, to furnish 1-($HOCH_2$)-1,4-BDO in 85% yield (isolated yield: 78%) and 2-Me-1,4-BDO in >94% yield, respectively (Fig. 3D, entries 1 and 4). 1-($HOCH_2$)-1,4-BDO (pentane-1,2,5-triol) has been produced from furfural or furfuryl alcohol in different ways (*38*). Itaconic acid has previously been hydrogenated to 2-Me-1,4-BDO using a Ru-Triphos catalyst (*39*). Citric acid and aconitic acid are C_6-TCA metabolites in the Krebs cycle (*17*), and their fermentation has previously been investigated (*15*, *16*). Although the time required was relatively long (120 hours) in both cases, the diol 2-Me-1,4-BDO was obtained uniformly in 45 to 47% yield (Fig. 3D, entries 2 and 3). The dehydration of citric acid may give *cis*- and/or *trans*-aconitic acid, which is transformed into itaconic acid upon decarboxylation. The subsequent hydrogenation of itaconic acid affords 2-Me-1,4-BDO (Fig. 2A).

Reaction of H_2 with miscellaneous DCAs and MCAs

Phthalic acid is a 1,4-DCA formed via the hydration of phthalic anhydride, which is a commodity chemical. Phthalic acid is an aromatic CA, and its CO_2H group is generally more inert to hydrogenation than that of aliphatic CAs (*8*, *39*, *40*). In addition, phthalic acid is difficult to hydrogenate to 1,2-bis(1,2-hydroxymethyl)benzene (BHB). Instead, phthalic acid tends to undergo dearomatic hydrogenation when heterogeneous catalysts are used (*40*). Even using a Ru-Triphos catalyst (1.5 mol %; P_{H2} = 8.5 MPa) (*41*), its ester, dimethyl phthalate, is preferentially hydrogenated to phthalide (PHT); only under specifically arranged strongly acidic conditions is BHB (78%), the major product (*41*). Neither homogeneous nor heterogeneous catalysts have achieved the selective 8*e* reduction/dehydration of the two adjacent CO_2H groups on the benzene ring in more than marginal yield. However, the selective hydrogenation of phthalic acid to BHB using Ir-**a** was successful when 1,4-dioxane was used as the solvent, giving BHB in 88% yield (11% PHT; Fig. 3E and tables S11 to S14). Reducing the reaction temperature from 160° to 140°C under otherwise identical conditions quantitatively furnished PHT (98%).

Levulinic acid is an important C_5-MCA that can be produced artificially from glucose/cellulose with promising scalability (*42*). Levulinic acid also undergoes hydrogenation using H_2 and Ir-**a** to give 1-Me-1,4-BDO (Fig. 2A) in 94% yield (Fig. 3D, entry 5). A Ru-Triphos catalyst showed similar reactivity (*39*).

Molecular insights into the behavior of the single-active site catalyst

Unlike with the deprotonation at the CH_2PiPr_2 moiety of Ru-**a**, which is facilitated when NaH is used, Ir-**a** seems to undergo spontaneous tautomerization upon heating in the absence of an alkali base. When a CH_3OD/tetrahydrofuran (THF)–d_8 solution of Ir-**a** was heated, the four hydrogen atoms of the two methylene units and the Ir—H were all replaced with deuterium atoms (Fig. 4A and figs. S6 to S9). The smooth H–D exchange at the methylene units is owing to thermal deprotonation and dearomatization, unlike the previous system where a base additive is needed for deprotonation (*32*, *33*). In contrast, that occurred on the Ir center under mild conditions was tentatively assigned to the hydricity-proticity interchange that occurs in parallel to Ir(III)–Ir(I) interconversion under near-neutral conditions. Similar H–D exchange has also been observed in a D_2O solution of a Cp*IrH(bpy) complex, but only under relatively acidic conditions (pD = 2.4 to 6.4) (*43*).

The facile tautomerization of Ir-**a**, which could lead to the dearomatization of the dipyridyl fragment, suggests that the hydrogenation of bpy might occur in the presence of H_2. To verify this hypothesis, in addition to testing the structural robustness of the resting state of the catalyst derived from Ir-**a**, Ir-**a** was activated under the conditions

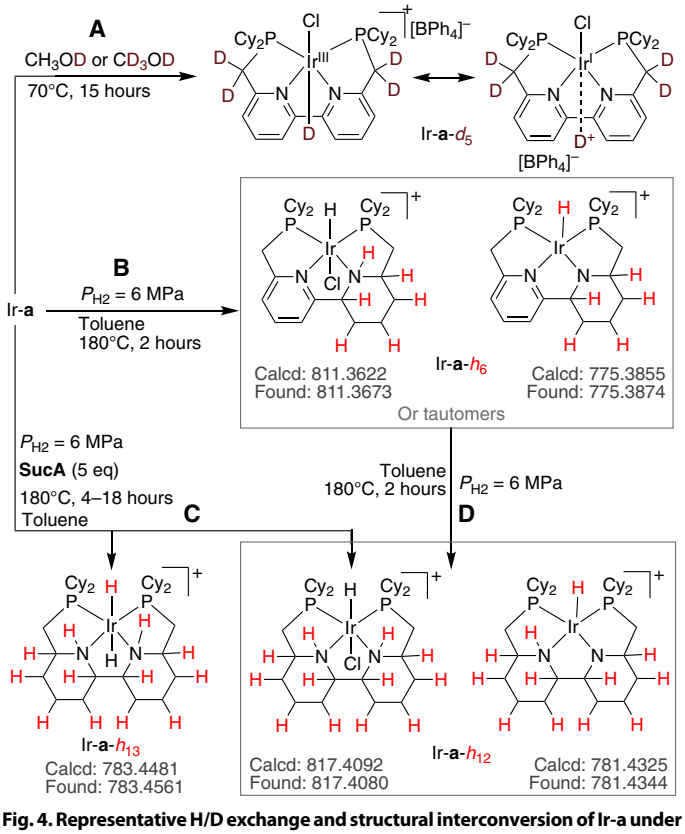

Fig. 4. Representative H/D exchange and structural interconversion of Ir-a under different reaction conditions. (**A**) Heating in deuterated alcohols without H_2. (**B**) Shorter heating with H_2. (**C**) Prolonged heating in the presence of a DCA with H_2. The values below each compound represent theoretical and experimental electron spray ionization–mass spectrometry values. (**D**) Prolonged heating with H_2.

used for the hydrogenation, and the resulting samples were subjected to electron spray ionization–mass spectrometry measurements (figs. S10 to S13). When Ir-**a** was preactivated for 2 hours in the absence of succinic acid, the mass spectra indicated that Ir-**a**-h_6 was the main intermediate (Fig. 4B), accompanied by the minor species Ir-**a**-h_{12} (Fig. 4D). The partial hydrogenation of bpy was detected. In contrast, heating the sample for an additional 2 hours gave Ir-**a**-h_{12} as the major product. Unlike in the case of Ru-**a** (*21*), however, the C—P bonds of Ir-**a** were not cleaved during these processes. When the preactivation of Ir-**a** was carried out in the presence of excess succinic acid, succinic acid was completely consumed, and Ir-**a**-h_{12} {Fig. 4C; ^{1}H nuclear magnetic resonance (NMR) [parts per million (ppm)]: δ −23.1 (1H, t, J = 16.1 Hz, ClIr*H*)} and Ir-**a**-h_{13} [Fig. 4C; ^{1}H NMR (ppm): δ −9.29 (2H, t, J = 13.8 Hz, IrH_2)] were the two major products observed, with the C—P bonds acting again as spectators. The species that catalyzes the hydrogenation would be produced via the incorporation of multiple hydrogen atoms into Ir-**a**.

It is highly likely that the Ir center of the catalyst is virtually coordinatively saturated with two apical ligands in *trans* configuration. The robustness of the catalyst is further demonstrated by the control experiment: After the hydrogenation of succinic acid for 18 hours, the catalyst even promoted effective hydrogenation of a second portion of GBL in one-pot operation (table S16). It could thus be feasibly concluded that two of the hydrogen atoms on the catalytic species "H(δ^-)—Ir—N—H(δ^+)" (*44*) are transferred directly onto olefins and the carbonyl groups of esters, anhydrides, and ketones; however, an alternative proton transfer pathway from the C—H bonds (*31*, *45*) of the Ir catalyst cannot be ruled out at this point. To the best of our knowledge, this is the first time that the Noyori-type bifunctional mechanism (*44*–*48*) has been experimentally invoked in the hydrogenation of CA anhydrides, assuming that the *trans* configuration of the induced (PNNP)Ir catalyst would be preserved from the precatalyst Ir-**a**.

One of the state-of-the-art heterogeneous catalysts for hydrogenation of both CAs and esters, Re/TiO_2 (*49*, *50*), was also tested for hydrogenation of succinic acid under similar conditions (Re = 1.5 mol %; P_{H2} = 6 MPa, T = 180°C, t = 18 hours) for comparison; however, the productivity and selectivity of the reaction was rather lower (1,4-BDO, 52%; GBL, 24%; THF, 24%; table S17). Similarly, malic acid was hydrogenated to GBL and THF, accompanied with a smaller amount of 1,4-BDO; tartaric acid was hydrogenated more selectively to GBL with maintaining the original C_4-chain (table S6). Negligible amounts of hydrogenation products were detected with aspartic acid. In contrast, Re/C (*50*) and Pd/Re/C (*51*) are less selective for hydrogenation of esters to the alcohols even under milder conditions.

In summary, this work demonstrates that a bespoke, structurally robust Ir complex with a tetradentate PNNP ligand can achieve the hydrogenative deoxygenation/deamination of a variety of biorenewable C_4—C_6 feedstocks. The conceptually new sterically confined Ir-bpy framework (i) prefers the uptake of H_2 relative to that of highly functionalized organic compounds, (ii) promotes reduction (hydricity) and dehydration (proticity), and (iii) retains the robust tetracoordinated organic-metal framework under strenuous hydrogenation conditions. This multifunctional, robust, single–active site molecular catalyst can be used for the hydrogenation of polyacids to polyols and for HDO and HDA reactions to give saturated carbon chains under weakly acidic conditions. The structural precatalyst/catalyst platform presented in this work could potentially be extended to develop more versatile catalysis for the hydrogenation and hydrogenolysis of thermodynamically stable and kinetically inert C—O and C—N single bonds, as well as other unsaturated bonds; these studies are currently in progress in our laboratory.

MATERIALS AND METHODS

For all information of experimental procedures and data, see the Supplementary Materials.

Representative hydrogenation procedure with Ir-a and sodium hydride

Succinic acid (118.1 mg, 1.0 mmol), Ir-**a** (10.9 mg, 0.01 mmol), sodium hydride (NaH; 55% paraffin dispersion, 2.6 mg, and 0.06 mmol), and a magnetic stirring bar were placed in a dried Teflon tube (21-ml capacity) (Fig. 3A, entry 4). The Teflon tube was inserted into an autoclave, which was closed tightly, evaporated in vacuum, and refilled with Ar gas. Anhydrous toluene (2.0 ml) was added to the mixture under a continuous flow of Ar, and the Ar inside the autoclave was purged with H_2 gas (P_{H2} = 1 MPa). The autoclave was pressurized by H_2 gas (P_{H2} = 6 MPa) at 25°C and heated at 180°C for 18 hours with stirring (800 rpm). The autoclave was cooled to 0°C in an ice-water bath. The reaction mixture was concentrated under a reduced pressure (ca. 35 mmHg, 50°C). The residue was diluted with dimethyl sulfoxide–d_6 and analyzed by ^{1}H NMR. The yields of GBL (5%) and 1,4-BDO (95%) were calculated on the basis of the integral ratio among the signals of these compounds with respect to an internal standard (mesitylene).

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/43/eabc0274/DC1

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Acknowledgments: We acknowledge K. Oyama, Y. Maeda, H. Okamoto, and H. Natsume for technical support. An active Re/TiO_2 was prepared and provided by T. Toyao and K. Shimizu at Hokkaido University, Japan. **Funding:** This work was supported by a Grant-in-Aid for Scientific Research on Innovative Area (18H04247, to S.S.) from MEXT and partially by the Asahi Glass Foundation (Step-up-grant, to S.S.) and by Scientific Research (B) (19H02713, to S.S.) from JSPS. **Author contributions:** S.Y. completed the research by extensive experiments and wrote a part of the manuscript and the full body of the Supplementary Materials. S.N. first synthesized the Ir complexes and found/developed primary parts of hydrogenation of C_4-DCAs. M.N. contributed to the other experimental parts. S.S. organized the overall research and wrote the manuscript. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

Submitted 2 April 2020
Accepted 10 September 2020
Published 23 October 2020
10.1126/sciadv.abc0274

Citation: S. Yoshioka, S. Nimura, M. Naruto, S. Saito, Reaction of H_2 with mitochondria-relevant metabolites using a multifunctional molecular catalyst. *Sci. Adv.* **6**, eabc0274 (2020).