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C6 Diacids from Homocitric Acid Lactone using Relay Heterogeneous Catalysis in Water

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Abstract: Conversion of renewable resources to the chemicals and materials needed for consumer products represents an exciting challenge for catalysis science. The BioAmber company currently produces succinic acid from corn sugar at its Sarnia, Ontario plant and is interested in producing additional bio-based chemical products. Here we discuss our initial progress on synthesizing C6 diacids from the sugar fermentation intermediate α -homocitric acid lactone using supported heterogeneous catalysts in water. Using high-throughput catalysis testing we have identified several promising catalysts for this process that yield different amounts of the three C6 diacids: adipate, 2-methylglutarate and 2-ethylsuccinate. We deduce that the process involves a relay of four different chemical reactions: dehydration, alkene isomerization, decarboxylation and alkene hydrogenation. DFT studies have been initiated in order to rationalize the activity and selectivity based on catalyst properties.

Keywords: relay catalysis, biomass conversion, decarboxylation, C6 diacids

Highlights: 1) A variety of metal catalysts (Pd, Pt, Rh, Ru) supported on carbon, metal oxides or weakly basic supports such as CaCO₃ and BaSO₄ effect the conversion of α -homocitric acid lactone (HCAL) to a mixture of C6 dicarboxylic acids.

2) The HCAL substrate contains three different carboxyl groups and high-throughput testing has identified catalysts that afford primarily adipic acid (Cu-Pd/C) or 2-ethylsuccinic acid (Pd/CaCO₃) or 2-methylglutaric acid (Ru/C).

3) One proposed reaction pathway involves a dehydration-isomerization-decarboxylation-hydrogenation relay.

4) Preliminary DFT studies identify the thermodynamic stabilities of HCAL, reaction intermediates and products.

1. Background

Conversion of renewable resources to chemicals and materials needed for consumer products represents an exciting challenge for catalysis science.[1,2,3] The BioAmber company currently produces succinic acid from corn sugar at its Sarnia, Ontario plant and is interested in producing additional bio-based chemical products. Here we discuss our initial progress on synthesis of C6 diacids from the sugar fermentation intermediate, α -homocitric acid lactone (HCAL), using supported heterogeneous catalysts in water.

Dibasic carboxylic acids are useful precursors to multi-use polymers such as Nylon 6,6 (cf. production of 3 M metric tons/yr of adipic acid). Current petrochemical routes to adipic acid, however, involve multiple steps and emissions of the greenhouse gas nitrous oxide.[4] As a result, there has been much activity in developing new routes from renewable resources. Verdezyne and Genomatica have developed biocatalysis routes using customized microbes and yeast strains[5,6] while Rennovia uses a two-step process that involves oxidation of fructose to glucaric acid.[7] Most recently, Zhang, Zhao and co-workers reported an impressive hybrid biocat-chemcat process for conversion of sugar beet residue to adipic acid that involves several high-yielding steps proceeding through a variety of carboxylic acid intermediates (Figure 1).[8]

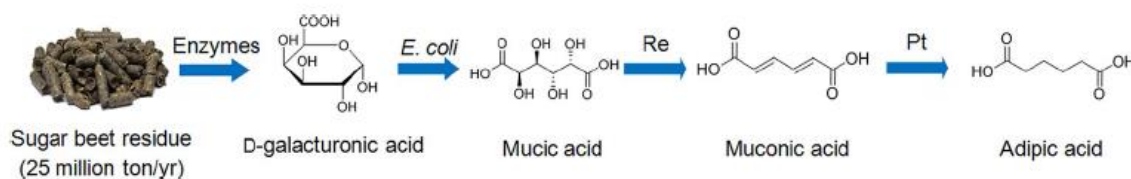


Figure 1. Biocat-chemcat route to adipic acid (see Ref [8]).

BioAmber has leveraged its expertise in the industrial biotechnology arena to accelerate the development of an engineered organism and fermentation process to convert biomass-derived sugars into the platform intermediate, HCAL.[9] The unsymmetrical structure of this intermediate provides a demanding test for selective decarboxylation to the three possible C6 diacid products: 2-ethylsuccinic acid (ESA), 2-methylglutaric acid (MGA) and adipic acid (AA), see Figure 2.

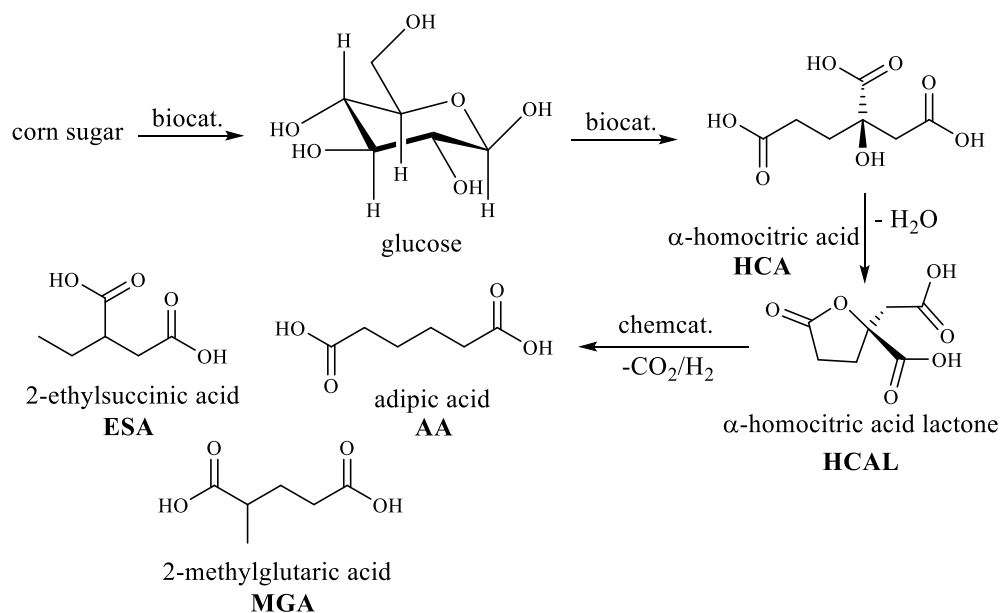


Figure 2. Hybrid biocat-chemcat scheme to produce C6 diacids.

Recent studies by van Haveren, Scott and co-workers demonstrated that Pd-, Ru- and Pt-based catalysts deposited on various supports (Al_2O_3 , activated carbon, CaCO_3 and BaSO_4) can be used for decarboxylation of citric acid in alkaline water for the synthesis of bio-based methacrylic acid with moderate activity and selectivity (41%; Figure 3).[10] With this precedent, we sought to optimize the first decarboxylation step using the unsymmetrical HCAL substrate under milder reaction conditions. In addition, we were keen to test a variety of heterogeneous catalysts with a view to achieving selective formation of each of the C6 diacids.

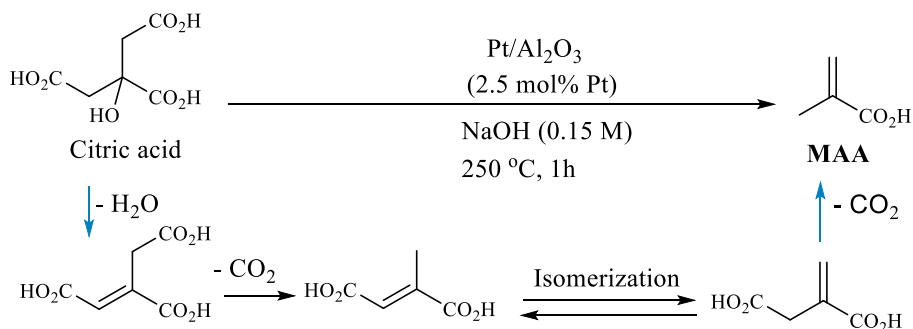


Figure 3. Pt-catalyzed conversion of citric acid to methacrylic acid in water (see Ref [10]).

2. Experimental

Heterogeneous catalysts were purchased from Johnson Matthey (Table 1). All catalysts were activated by heating at 180°C for 2 h under 400 psi N_2 , then 2 h under 200 psi H_2 . The C7

tricarboxylic acid, 1,2,4-butanetricarboxylic acid, methanol and dimethylsulfoxide were all purchased from Sigma-Aldrich and used as received. The HCAL substrate was precipitated from fermentation broths using the previously reported procedure.[11] For the high-throughput experiments the catalysts were dispensed by Unchained Labs' Freeslate system using the SV-vial technology whereas liquid reagents and solutions were dispensed by pipette. Reactions were conducted in 1.2 mL glass shell vials equipped with parylene-coated stir bars in 96-well aluminum plates, which were sealed with a PFA sheet, rubber gasket, and top stainless steel plate.

Table 1. Heterogeneous catalysts used for conversion of HCAL to C6 diacids

	Support	Loading
Pd	carbon	5%
Pd	carbon (sulfided)	5%
Pd	alumina	5%
Pd	CaCO ₃	5%
Pd	BaSO ₄	5%
Pt	carbon	3%
Pt	carbon (sulfided)	5%
Pt	alumina	5%
Rh	carbon	5%
Rh	alumina	5%
Ru	carbon	5%

HPLC analysis was performed on an Agilent 1100 system equipped with a DAD detector, GC-FID analysis on an Agilent 6850 instrument, and GC/MS analysis on an Agilent 6890/5975 instrument.

Typical procedure for HCAL conversion to diacids. The aqueous substrate and catalyst mixture was pressurized with hydrogen (or H₂/N₂ mixture) and heated at 180°C for 16 h after which the products were derivatized to the methyl esters using methanol and concentrated sulphuric acid and analyzed by GC-MS and GC-FID. Quantitative analysis was achieved using response factors calculated from solutions of the three derivatized C6 diacids and C7 triacid.

Reaction scale-up

Several promising catalysts were also employed under locally optimized reaction conditions in a 350 mL Autoclave Engineers autoclave. Products were characterized from the crude reaction mixtures by HPLC using refractive index and mass spectrometric detectors and as their methyl esters using GC-MS/GC-FID analysis.

Computational details

The first-principles computations are performed using Density Functional Theory (DFT) as implemented in the Gaussian09 program package[12] All structures are optimized in water using the M06-2X[13] functional applying the 6-311G** basis set. The Polarizable Continuum Model (PCM) is exploited to model the influence of bulk water.[14] The electronic energy is refined by single-point energy calculations using a larger basis set def2-QZVPP[15] and SMD solvation model[16] Gibbs free energies are obtained at 180°C and 1 atm according to standard statistical mechanics based on harmonic frequencies and rigid rotator.

3. Results and Discussion

Initial studies using **HCAL** in methanol solvent and 0.5 mol% of 5% Pd/C catalysts under 200 psi of H₂ showed little conversion at 100°C. Conducting the reaction at 180°C gave the trimethyl ester of the 1,2,4-butanetricarboxylic acid hydrogenolysis product (**TCA**) after 16 h. Switching to water solvent accelerated the reaction considerably with full conversion to the triacid observed after 4 h at 150°C. Interestingly, the 5% Pd/C catalyst also afforded some C₆ diacids that became the major products employing the sulfided 5% Pd/C catalyst (180°C, 200 psi H₂, 16h, **TCA:AA:ESA:MGA** ratio = ca. 1:2:6:0; Fig. S1). In contrast, the 5% Pd/CaCO₃ catalyst favoured ESA over AA (Fig. S2). Pt catalysts on carbon and alumina supports gave moderate diacid:triacid ratios with nearly equal amounts of AA and ESA (Fig. S3). Unlike Pd, the sulfided Pt/C catalyst gave poor activity and selectivity, yielding nearly equal amounts of the three diacids (Fig. S4). While similar results were obtained with 5% Rh/C catalyst, the 5% Ru/C was unique in forming **MGA** as the major product albeit with some additional unidentified by-products (Fig. S5).

Given the unique properties of the sulfided Pd/C catalyst, we investigated the addition of dimethylsulfoxide under our reaction conditions using a standard Pd/C catalyst (Figure 4). At the optimal 20% DMSO-water mixture the triacid to diacids ratio is greatly reduced.

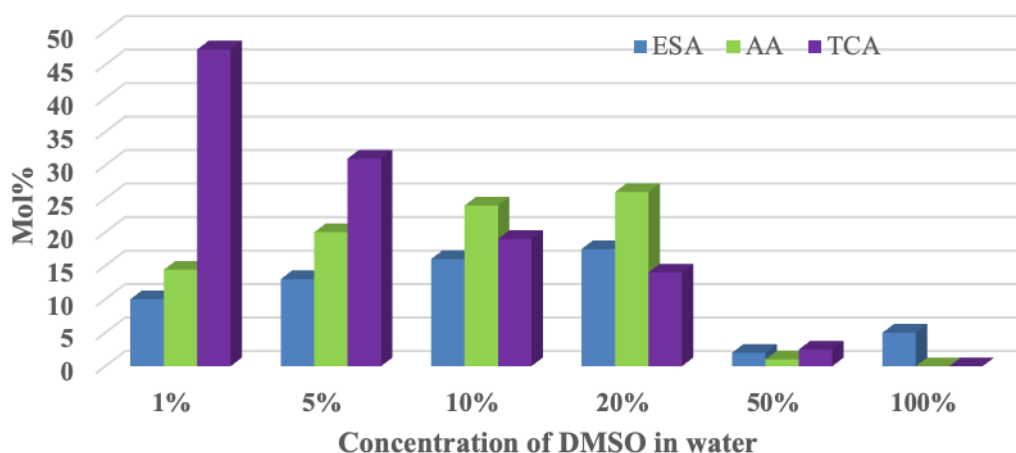


Figure 4. Activity and selectivity of 1 mol% Pd/C catalyst in water-DMSO mixtures (180°C, 16 h, 450 psi H₂)

Although the van Haveren-Scott work with citric acid showed the best performance in alkaline aqueous solution (one equivalent of NaOH per substrate)¹⁰ comparing the monosodium homocitrate salt with the **HCAL** feed showed reduced activity and selectivity with the former (Figure 5). In addition, using **TCA** as reaction feed afforded no products with the exception of the sulfided Pd/C catalyst that produced a small amount of C₆ diacids, demonstrating that **TCA**

is an inert product and not an intermediate under our reaction conditions.

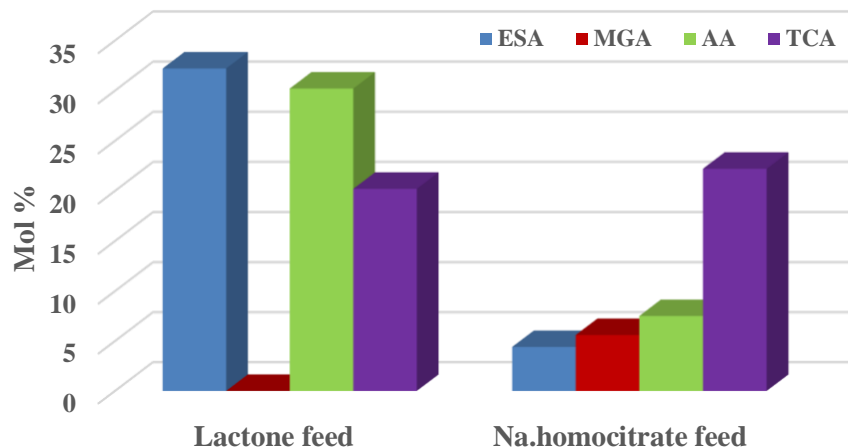


Figure 5. Products derived from lactone vs. sodium homocitrate feed using 1 mol% Pd/CaCO₃ (180°C, 24 h, 450 psi H₂)

A postulated mechanism is shown in Figure 6, followed by the corresponding thermodynamic profile computed at the DFT level (see computational details) in Figure 7.

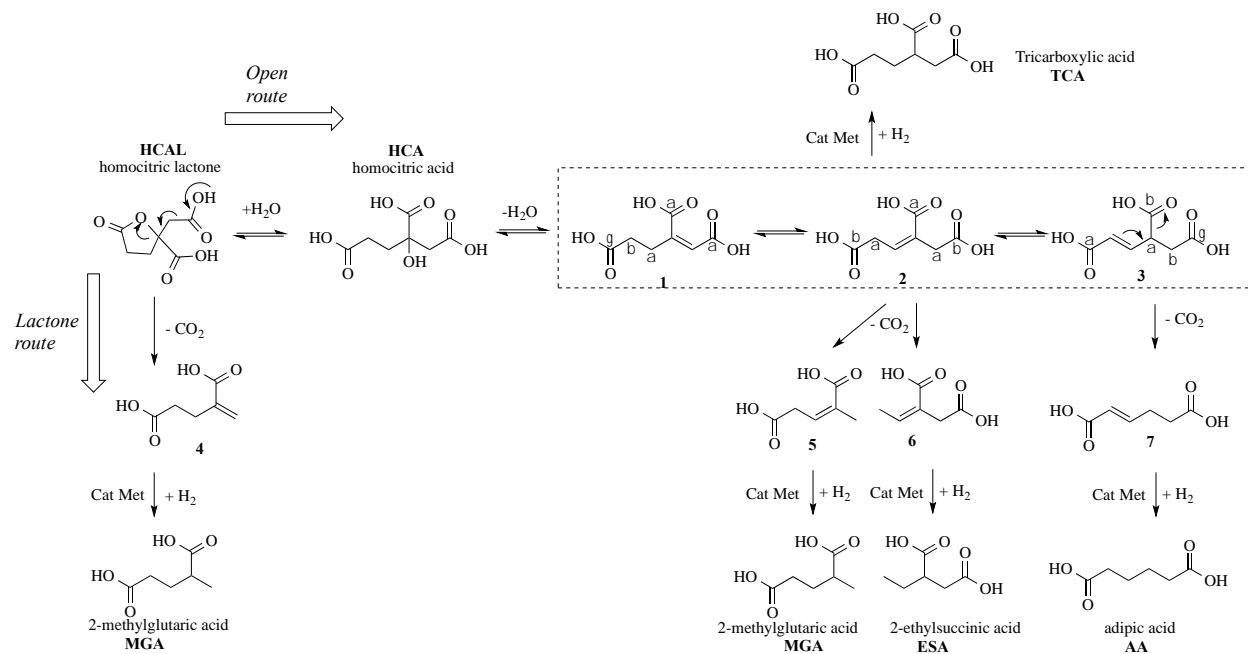


Figure 6. Proposed mechanism for the aqueous-phase hydrogenation of homocitric acid lactone (HCAL).

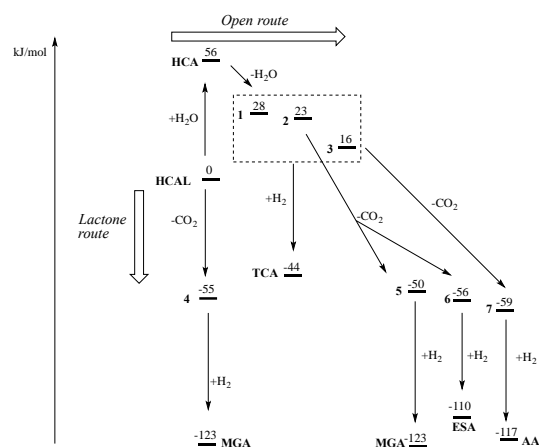


Figure 7. Computed Gibbs Free Energy profile at 180°C, 1atm and referred to **HCAL** and water, corresponding to the postulated mechanism shown in Figure 6.

As it is shown in Figures 6 and 7, two main routes are postulated: (i) a *lactone route* that starts with the decarboxylation of the homocitric lactone (**HCAL**) (ii) a *open route*, that requires first the hydration of the lactone into its corresponding acid **HCA**.

Thermodynamically, the decarboxylation of the lactone **HCAL** is favoured over its hydration. The resulting unsaturated di-carboxylic acid **4** will be easily hydrogenated into a saturated dicarboxylic acid under a pressure of hydrogen and in presence of a Pd catalyst. This route yields to methylglutaric **MGA**. While this is thermodynamically favored, this mechanism cannot explain the observed **TCA** nor the adipic acid **AA** and ethylsuccinic acid **ESA**.

The hydration of the reactant lactone **HCAL** induces its opening into the homocitric acid **HCA**. This homolog of citric acid can be then dehydrated into an unsaturated tri-carboxylic acid. Three isomers are possible (**1**, **2**, and **3**). Isomer **3** is slightly (8 kJ/mol) more stable than the other ones. All three isomers can be hydrogenated into the unwanted tri-carboxylic **TCA** on hydrogenation catalysts such as Pd. Otherwise, isomer **2** can also undergo first a decarboxylation of the carboxylic group in beta position of C=C double bond, yielding the unsaturated di-carboxylic acids **5** or **6**. Then, these intermediates can be hydrogenated into methylglutaric acid **MGA** and the ethylsuccinic acid **ESA**, respectively. Following a similar route, the most stable isomer **3** gives the adipic acid **AA** through **7**. Since **TCA** is less stable than the intermediates **5**, **6**, and **7** and much less stable than **AA**, **MGA** and **ESA**, the decarboxylation is thermodynamically favored over the hydrogenation. However, **TCA** can be found in all experimental conditions, while the di-carboxylic acids are more difficult to obtain. In other words, the competition between the decarboxylation and the hydrogenation of the isomers **2** and **3** is a kinetically controlled step. This is in agreement with further experimental findings mentioned above: Switching from Pd/C to a sulfided catalyst Pd-S/C limited the ability of the catalyst to perform the hydrogenation step and the selectivity towards dicarboxylic acids was improved.

To probe the competition between decarboxylation and hydrogenation in more detail, we

conducted the reaction in the absence of H₂ and in N₂-H₂ mixtures. In the absence of H₂ the activated Pt/C catalyst produced mainly C₆ diacids at the expense of TCA (Fig. S6) whereas the Pd/CaCO₃ and Pd/BaSO₄ catalysts also yielded unsaturated C₆ diacid and its lactone (Figs. S7,8). Using the latter catalyst with an N₂/H₂ mixture led to increases in both activity and selectivity to AA (Figure 8, left). This is in good agreement with the postulated competition between decarboxylation and hydrogenation, given that the formation of AA, ESA and MGA actually requires an H₂ source.

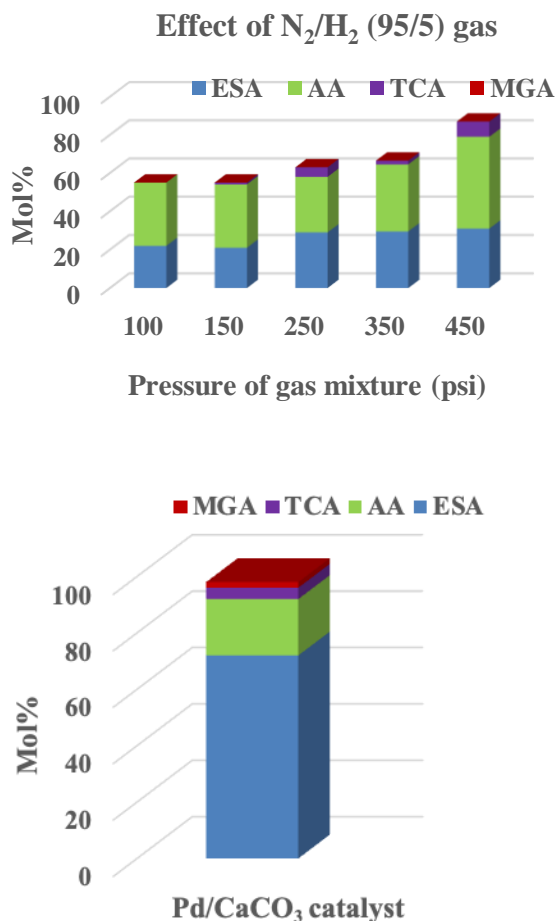


Figure 8. Minimizing tricarboxylic acid production using N₂/H₂ gas mixture in presence of Pd/CaCO₃ catalyst (left). Reaction products from scale-up reaction (right).

Finally, in a scale-up reaction using a 350 mL autoclave, 50 mL of 0.12M lactone in H₂O at 200 C and 34.5 bar H₂ (increased to 54 bar) for 16 h gave >75% C₆ diacid products.

Current studies are focused on custom made bimetallic alloy catalysts and a systematic combination of experimental and computational chemistry approaches to further understand effects of catalysts on relative rates of alkene intermediate isomerization, decarboxylation and

hydrogenation reactions.

4. Conclusions

This work confirms that the decarboxylation of tricarboxylic acid lactones occurs under milder conditions than mono- or diacids[10,11] much like Dumesic's work with pyrones.[12] The preliminary results summarized herein[13] indicate some selectivity control over the production of C6 diacids from the sugar fermentation intermediate, α -homocitric acid lactone, a process that could provide additional bio-based feedstocks for the 'green' polymer industry.

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Appendix A. Supplementary Data

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