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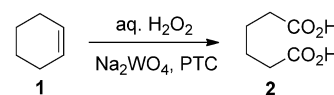
# Continuous-Flow Synthesis of Adipic Acid from Cyclohexene Using Hydrogen Peroxide in High-Temperature Explosive Regimes

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Adipic acid is the basic building block for a wide variety of products and it is by far the most important aliphatic dicarboxylic acid from an industrial perspective.<sup>[1]</sup> About 3 million tonnes of adipic acid are produced annually worldwide, with the majority used as monomer for the synthesis of nylon 6,6. In addition, adipic acid is a raw material for the production of polyesters, polyurethanes, low-temperature synthetic lubricants, plasticizers, adiponitrile, and is used as a flavoring substance and gelling aid in food products.<sup>[1]</sup>

Most of the adipic acid is synthesized in two steps from cyclohexane.<sup>[1]</sup> Cyclohexane is first oxidized with air to a mixture of cyclohexanol and cyclohexanone (KA oil), generally in the presence of a cobalt catalyst or a combination of cobalt catalyst and anhydrous *meta*-boric acid. The KA oil is then converted to adipic acid through a process developed in essence already in the 1940s.<sup>[1]</sup> It involves oxidation of the KA oil with 40–60% nitric acid in the presence of copper and vanadium catalysts, removal of nitrogen oxides and water and, finally, crystallization of adipic acid from the nitric acid. Glutaric and succinic acid, along with pentanoic and hexanoic acid, are formed as side products and further refining of adipic acid, typically recrystallization from water, is needed to attain polymer-grade material.<sup>[1]</sup> Carbon- and nitrogen oxides are formed as major gaseous side products, and, whereas NO and NO<sub>2</sub> can be recovered almost completely and returned to the process as nitric acid, N<sub>2</sub>O (0.3 kg of N<sub>2</sub>O per kg of product) cannot be recovered and has to be subjected to downstream treatment.<sup>[1,2]</sup>

N<sub>2</sub>O is a major greenhouse gas and air pollutant, and even though virtually all adipic acid producers employed N<sub>2</sub>O abatement technologies since 1996 to decrease N<sub>2</sub>O emissions, the production of adipic acid is still a major industrial source of emitted N<sub>2</sub>O.<sup>[1,2]</sup> In 1998 Sato, Aoki, and Noyori demonstrated the direct oxidation of cyclohexene to adipic acid using aqueous hydrogen peroxide under organic solvent-free conditions (Scheme 1).<sup>[3]</sup> There is increasing interest in H<sub>2</sub>O<sub>2</sub> as a green oxidation reagent, not only due to stricter environmental regulations forcing the chemical industry to reduce or eliminate environmental pollution, but also because the chemical industry has learnt to exploit hydrogen peroxide in a safe and efficient



**Scheme 1.** Direct oxidation of cyclohexene to adipic acid using hydrogen peroxide.<sup>[3,6,7]</sup>

manner.<sup>[4,5]</sup> Noyori and co-workers accomplished the oxidation of cyclohexene to adipic acid by employing Na<sub>2</sub>WO<sub>4</sub> × 2 H<sub>2</sub>O as catalyst and [CH<sub>3</sub>(*n*-C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>N]HSO<sub>4</sub> as a phase-transfer catalyst (PTC).<sup>[3]</sup> Using 1 mol% of catalyst, 1 mol% of PTC, and 4.4 equiv (10% excess) of 30% aqueous H<sub>2</sub>O<sub>2</sub>, the transformation of cyclohexene to adipic acid was completed within 8 h at 90 °C.<sup>[3]</sup> Slightly modified protocols were published since then and some became popular undergraduate laboratory procedures to illustrate concepts of green chemistry and phase-transfer catalysis to students.<sup>[6,7]</sup>

A main obstacle for an industrial application of this direct oxidation route from cyclohexene to adipic acid is the requirement for an ammonium hydrogensulfate PTC to achieve sufficient contact between the hydrophobic substrate and the hydrophilic reagent and catalyst (peroxytungstate is soluble in water but immiscible with cyclohexene).<sup>[8]</sup> However, it was demonstrated that the PTC can be replaced by organic ligands, which coordinate onto the tungstate catalyst.<sup>[6b,c]</sup> In addition, the preparation of adipic acid from cyclohexene and aqueous H<sub>2</sub>O<sub>2</sub> in the absence of any PTC was disclosed.<sup>[6d,9]</sup> This transformation was recently performed in continuous stirred tank reactors (CSTRs) on a pilot scale with tungstic acid (H<sub>2</sub>WO<sub>4</sub>) as the catalyst employing H<sub>2</sub>SO<sub>4</sub> and H<sub>3</sub>PO<sub>4</sub> as promoters.<sup>[9]</sup> Unfortunately, the oxidation to adipic acid required a reaction time of 10 h at 90 °C and, thus, rather large reactors are necessary to achieve industrially relevant productivities.

A continuous process employing microreactors could potentially overcome limits associated with this reaction by improving interfacial mass transfer and by allowing unusually harsh process conditions (i.e., high temperature/pressure) in a safe and controllable manner, thereby reducing reaction time and increasing volume productivity (mols of product per unit volume of reactor).<sup>[10,11]</sup> In this communication we present our investigations into a high-temperature continuous-flow synthesis of adipic acid from cyclohexene, cyclohexanol and cyclohexanone using aqueous H<sub>2</sub>O<sub>2</sub> and tungstic acid as catalyst. No PTC or other additives were required, greatly simplifying workup (the PTC tends to coprecipitate with adipic acid) and reducing production cost.

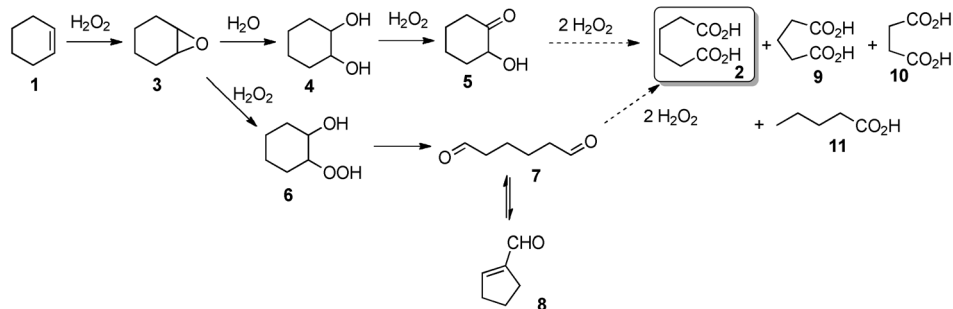
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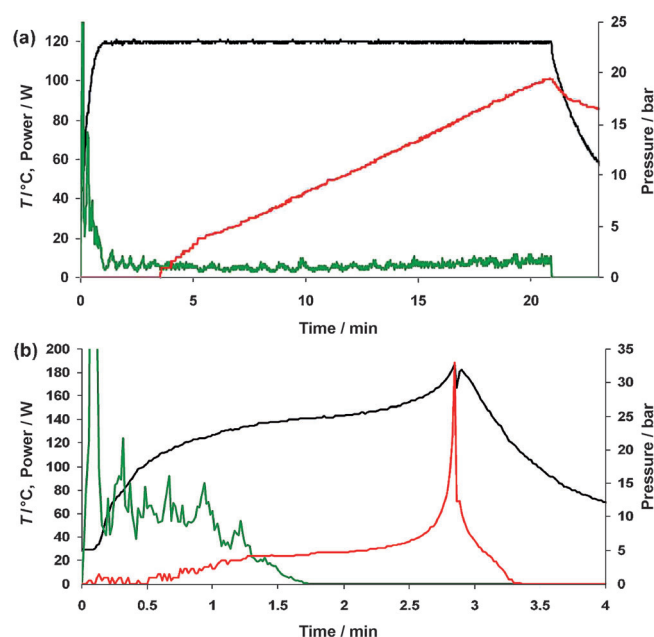
Tungstic acid was used as the precatalyst, as its catalytic efficiency for the oxidation of cyclohexene in the absence of a PTC was shown in previous studies.<sup>[9,12]</sup> Tungstic acid is basically insoluble in water, but in aqueous H<sub>2</sub>O<sub>2</sub> it slowly forms a water-soluble peroxy-complex (presumably the catalytically active species). In contrast, the solubility of cyclohexene in water is exceedingly small (250 mg L<sup>-1</sup>) and the oxidation of cyclohexene therefore necessitates an interphase mass transfer before the reactants come into contact. The quantity of reactant transferred between the phases is proportional to the interfacial area per unit volume, so that creation of interfacial area is crucial for achieving sufficient mass transfer for the reaction to occur and to minimize unwanted side reactions in the homogeneous phase.

Following the “microwave-to-flow” paradigm,<sup>[13]</sup> initial optimization reactions in a high-temperature regime were performed in a microwave batch reactor in sealed, pressure-resistant glass vials.<sup>[14,15]</sup> Unfortunately, sufficient stirring could not be achieved in standard 10 mL cylindrical reaction vessels, and the organic cyclohexene phase remained essentially undisturbed on top of the aqueous phase (Figure S1 in the Supporting Information). In fact, experiments in 10 mL microwave vials with 4 mmol of cyclohexene and 4.4 equiv of 25% aqueous H<sub>2</sub>O<sub>2</sub> (reaction volume ≈ 2.5 mL) repeatedly led to a rapid increase of pressure due to unproductive decomposition of H<sub>2</sub>O<sub>2</sub> in the aqueous phase (Figure 1). Decomposition of H<sub>2</sub>O<sub>2</sub> is a highly exothermic process (ca. 23 kcal mol<sup>-1</sup> at 25 °C), causing the temperature of the decomposing solution to rise if the generated heat is not effectively dissipated to the surroundings.<sup>[4]</sup> Such a rise in temperature increases the rate of decomposition (about 2.3 times for a temperature rise of 10 °C),<sup>[4]</sup> and a thermal runaway with large volumes of evolving oxygen can follow (Figure 1). However, efficient agitation was readily achieved in 30 mL microwave vials with approximately 5 mL reaction volume (Figure S1 in the Supporting Information). In these vials 8 mmol of cyclohexene were oxidized to adipic acid using 4.4 equiv of 25% H<sub>2</sub>O<sub>2</sub> at 130 °C in 94% selectivity (GC–MS analysis, see Table S1 in the Supporting Information) without an appreciable increase of pressure during the reaction. The reaction temperature could be even increased to 150 °C without reducing selectivity for adipic-acid formation and without noticeable unproductive decomposition of H<sub>2</sub>O<sub>2</sub> (internal pressure was constant at ≈ 9 bar).

The mechanism of this remarkable transformation is not entirely certain, but a reaction pathway consisting of four distinct oxidation reactions (epoxidation, alcohol oxidation, Baeyer–Villiger oxidation, and aldehyde oxidation; see Figure S2 in the Supporting Information) was suggested by Noyori et al.<sup>[3]</sup> In our microwave batch experiments, the rate-determining reaction step was clearly the initial oxidation of the cyclohexene



**Scheme 2.** Formation of adipic acid from cyclohexene and H<sub>2</sub>O<sub>2</sub> is generally accompanied by the formation of glutaric, succinic and valeric acid.<sup>[3,6]</sup> Epoxidation of alkenes and oxidation of alcohols to ketones with H<sub>2</sub>O<sub>2</sub> and tungstates as catalysts are well documented.<sup>[3b]</sup>



**Figure 1.** Temperature [*T* (IR) —], pressure (*p* —) and microwave power (*P* —) profiles for reactions in a 10 mL sealed microwave vial at (a) 120 and (b) 140 °C (600 rpm stirring rate). (a) Continuous decomposition of H<sub>2</sub>O<sub>2</sub> was observed at 120 °C (run was manually aborted after 20 min); (b) a runaway decomposition led to a rapid increase in internal pressure at a temperature of 140 °C (microwave power reduced to 0 W at ≈ 1.6 min; run was automatically aborted at 30 bar, and the reaction mixture cooled with compressed air).<sup>[14,15]</sup>

and only very small or trace amounts of intermediates were detectable throughout the reaction using GC–MS analysis. The most prominent intermediate was cyclohexanediol (**4**), but also 2-hydroxycyclohexanone (**5**), cyclopentenecarboxaldehyde (**8**), and adipaldehyde (**7**) were detected in trace amounts (Scheme 2). **8** is evidently formed from **7** through an aldol condensation, whereas **7** is probably derived from a ring opening of the epoxide with H<sub>2</sub>O<sub>2</sub> as the nucleophile and subsequent decomposition of the resulting 2-hydroxy peroxide.<sup>[16]</sup> The main side product formed in the H<sub>2</sub>O<sub>2</sub> oxidation of cyclohexene was glutaric acid (**9**), as already observed by Noyori et al.<sup>[3]</sup> In addition, small amounts of succinic (**10**) and valeric acid (**11**) were detected in agreement with previous observations (Scheme 2).<sup>[6c–e,9]</sup>

Using 1% of  $\text{H}_2\text{WO}_4$  and 4.4 equiv of  $\text{H}_2\text{O}_2$  (10% excess), 60 min at  $140^\circ\text{C}$  were required to obtain a complete consumption of cyclohexene and an optimum yield of adipic acid (92% GC–MS selectivity; Table S2 and Figure S3 in the Supporting Information). The acid crystallized upon cooling of the reaction mixture as a white powder and was isolated in analytically pure form by filtration and washing with cold 1 N HCl ( $\approx 3$  mL) in 64% product yield. Due to the rather high solubility of adipic acid in water ( $0.53\text{ mol L}^{-1}$  at  $25^\circ\text{C}$ , pH 2.34), significant amounts of acid were lost into the aqueous phase and concentration of the crude reaction mixture, filtration, and washing with cold 1 N HCl provided somewhat better yields (73%). It should be emphasized that the selectivity and yields of adipic acid obtained with this high- $T/p$  protocol ( $140^\circ\text{C}$ ) were comparable to those obtained in control experiments under traditional Noyori reaction conditions in the presence of a PTC (59% isolated yield after 8 h reaction time at  $90^\circ\text{C}$ ; see Table S2 and Figure S4 in the Supporting Information).

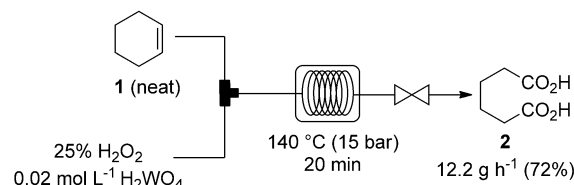
Decreasing the amount of catalyst below 1% reduced the reaction rate, whereas no significant effect on the selectivity was observed. Decreasing/increasing the amounts of  $\text{H}_2\text{O}_2$  below/above 4.4 equiv of  $\text{H}_2\text{O}_2$  decreased the yield of adipic acid. The addition of  $\text{H}_3\text{PO}_4$  as acidic promoter and stabilizing agent for  $\text{H}_2\text{O}_2$ <sup>[9]</sup> had no effect on the purity of the reaction or on the reaction rate (for more optimization reactions under microwave batch conditions see Tables S3–S6 in the Supporting Information).

Even though the reaction described above proceeded well on a small scale (8 mmol), it should be emphasized that  $\text{H}_2\text{O}_2$  is a very reactive chemical and an extremely powerful oxidizer that forms highly dangerous peroxygen compounds with organic substrates (such as ketones). The decomposition of  $\text{H}_2\text{O}_2$  to  $\text{H}_2\text{O}$  and  $\text{O}_2$  is very exothermic and can accelerate rapidly. The released  $\text{O}_2$  increases internal pressure and gives rise to oxygen-rich, flammable atmospheres with low ignition energies.<sup>[4]</sup>

Compared to conventional batch reactors, flow systems with small-diameter channels or capillaries offer enhanced heat and mass transport and allow safe operation of reactions in an extended range of operation conditions, for example, the explosive region.<sup>[10,17,18]</sup> Furthermore, rapid mixing and excellent heat transfer can be maintained up to high production scales.<sup>[17b]</sup> On the other hand, however, the exceptionally high surface-to-volume ratio in microstructured flow systems may entail pronounced reactor-wall effects and unexpected/unwanted side and degradation reactions.<sup>[19]</sup> Several metal contaminants (e.g. Fe, Cu, Cr, or Mn ions) initiate the decomposition of  $\text{H}_2\text{O}_2$ , and heterogeneous decomposition can occur on all material surfaces.<sup>[20]</sup> Therefore, only a limited selection of materials are sufficiently compatible with  $\text{H}_2\text{O}_2$  and suitable for high temperature or long-term contact.

For our continuous-flow reactions, a simple flow system free of metal parts in the heated reaction zone was assembled (see Figure S5 in the Supporting Information). The system consisted of two glass syringe pumps, a T-mixer, a residence tube made of perfluoroalkoxy (PFA; 0.8 mm inner diameter, 50 m length,  $\approx 25$  mL internal volume), and an adjustable stainless steel

back pressure regulator (BPR, set to 15 bar). The residence tube was coiled onto a stainless steel cylinder and heated in a GC oven to the desired temperature. For adipic-acid generation, the neat cyclohexene (feed A) and a solution of tungstic acid in 25% aqueous  $\text{H}_2\text{O}_2$  (feed B;  $0.02\text{ mol L}^{-1}\text{ H}_2\text{WO}_4$ ) were pumped as two separate streams into the T-mixer at flow rates that established the desired stoichiometry of  $\text{H}_2\text{O}_2$  (Figure 2).



**Figure 2.** Oxidation of cyclohexene under continuous flow conditions. See the Experimental Section for further details.

The resulting two-phase liquid–liquid reaction system entered the PFA residence tube in well-defined liquid–liquid segments.<sup>[21]</sup> However, after several minutes residence time, the mixture became completely homogeneous as the cyclohexene was oxidized to more polar, better soluble products. The mixture passed the residence tube and left the reactor through the BPR, which was held at  $80^\circ\text{C}$  to prevent premature precipitation of adipic acid and clogging of the system. After the processed mixture left the BPR, the adipic acid immediately precipitated and the pure acid was isolated by filtration and washing with cold 1 N HCl as described above. At a reaction temperature of  $140^\circ\text{C}$ , the selectivities obtained in these flow reactions were comparable to those obtained in the microwave batch experiments (see Figure S6 in the Supporting Information), but complete oxidation of cyclohexene to adipic acid was attained already after 20 min residence time and the pure acid could be isolated in 63% yield after filtration ( $\approx 10$  mmol scale, 74% after a concentration step, see Table S7 in the Supporting Information for further details). In fact, cyclohexene was completely consumed after residence times as short as 5 min, but reaction intermediates (i.e., **4** and **5**) were detectable under these conditions. The higher turnover rate of cyclohexene achieved in the flow system as compared to the batch system can be rationalized by a superior mass-transfer performance in the small diameter channel and hence increased oxidation rate. The reaction was then ran for 1 h, processing 9.5 g (116 mmol) of cyclohexene ( $140^\circ\text{C}$ , 20 min residence time) to provide 12.2 g (84 mmol; 72%) of pure, crystalline adipic acid after a simple filtration step (see Experimental Section). Increasing the reaction temperature to  $150^\circ\text{C}$  or increasing the concentration of  $\text{H}_2\text{O}_2$  from 25% to 38% decreased the purity of the reaction and the yields of adipic acid (Table S7 in the Supporting Information).

Finally, the continuous-flow protocol was extended to cyclohexanol and cyclohexanone as substrates without reoptimization of the reaction conditions (the stoichiometry of  $\text{H}_2\text{O}_2$  was adjusted to 3.3 equiv for cyclohexanone).<sup>[12]</sup> Acid-catalyzed reactions of  $\text{H}_2\text{O}_2$  with ketones are generally quite complex and

yield several organic peroxides as initial products.<sup>[4]</sup> Some of these are highly dangerous and may be stable enough for dangerous concentrations to accumulate. The continuous-flow oxidation of cyclohexanol and cyclohexanone at 140 °C with 1 mol% of H<sub>2</sub>WO<sub>4</sub> yielded adipic acid as the final product in selectivities of around 80%.<sup>[22]</sup> As for reactions with cyclohexene, the adipic acid crystallized immediately after the BPR and was isolated through filtration and washing with cold 1N HCl. The main side products formed in the oxidation of cyclohexanol and cyclohexanone were again **9**, **10**, and **11**, but also small amounts of hexanoic acid were detected (see Tables S8 and S9 in the Supporting Information). With residence times of 60 min at 140 °C, pure adipic acid was isolated through simple filtration in 55 and 50% product yield for the continuous oxidation of cyclohexanol and cyclohexanone, respectively ( $\approx$  10 mmol scale, Table S10).

In conclusion, an intensified process for the oxidation of cyclohexene, cyclohexanol and cyclohexanone to adipic acid using H<sub>2</sub>O<sub>2</sub> as green oxidizing agent in a high-temperature/pressure process window has been presented. The reaction was performed employing tungstic acid as catalyst and did not require a phase-transfer catalyst or any other additive. A scalable continuous-flow approach utilizing a microstructured flow reactor was devised, which allowed safe operation and intensification of the process owing to the exceptional mass-transport capabilities of small-diameter channels. The high-temperature/pressure continuous-flow process demonstrated herein may bring significant benefits in terms of process efficiency, capital investment, operating expense, and process safety compared to a traditional batch process,<sup>[23]</sup> and may present an interesting alternative to the current industrial process for adipic acid synthesis, provided cost of H<sub>2</sub>O<sub>2</sub> can be reduced and/or the regulations regarding N<sub>2</sub>O emissions become more stringent.

## Experimental Section

The continuous flow setup consisted of a two-feed syringe pump system (Asia, Syrris), a coil made of PFA, and a manually adjustable back pressure regulator (Swagelok pressure regulator; Figure 2). A PFA coil having an inner diameter of 0.8 mm was utilized for the study (25 mL); the coil was heated to the desired temperatures (140 and 150 °C) in a GC oven. Feed A contained the neat substrate (cyclohexene, cyclohexanone, or cyclohexanol), feed B contained a mixture of the H<sub>2</sub>O<sub>2</sub> solution (25% or 38%) and tungstic acid (0.02 mol L<sup>-1</sup>). The flow rates of the individual pumps were selected to obtain the desired stoichiometries (3.3 and 4.4 equiv) as well as residence times (10, 20, 30, and 60 min), applying total flow rates between 0.42–2.5 mL min<sup>-1</sup>. Optimization runs were performed on an approximately 10 mmol scale. After the reaction, samples were analyzed using GC–MS (for details see the Supporting Information), and the processed reaction mixture was cooled for approximately 2 h at 0 °C. The resulting precipitate was separated through filtration, washed with 3 mL of (0 °C) 1 N HCl, and the product dried over night at 50 °C. The long run was performed on a 116 mmol scale. The precipitate after cooling the reaction mixture was separated through filtration, washed with 8 mL of cold 1 N HCl, and the product was dried over night at 50 °C to produce 12.2 g analytically pure adipic acid.

## Acknowledgements

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**Keywords:** adipic acid • hydrogen peroxide • microreactor • oxidation • process intensification

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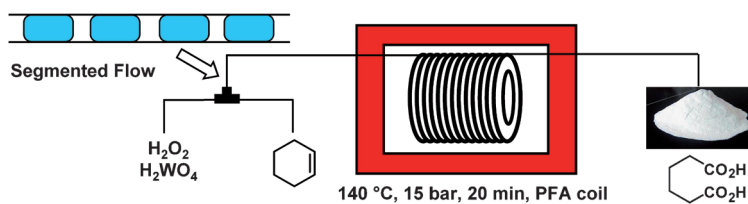
# COMMUNICATIONS

M. Damm, B. Gutmann, C. O. Kappe\*

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## Continuous-Flow Synthesis of Adipic Acid from Cyclohexene Using Hydrogen Peroxide in High-Temperature Explosive Regimes



**Safe only in a microreactor!** The synthesis of adipic acid from cyclohexene by tungstic acid-catalyzed oxidation using hydrogen peroxide following the classical Noyori protocol can be accomplished in good yields with residence

times as short as 20 min at 140 °C using a safe and scalable microreactor environment. Under these intensified conditions the use of a phase-transfer catalyst is not required.