Supplementary Information

One-Pot Mechanochemical Hydrogenation and Acetylation of 4-Nitrophenol to 4-Aminophenol and Paracetamol

Jimin Park,[abe] Jacob S. Maier,[a] Caria Evans,[bce] Marta Hatzell,[ad] Stefan France,[bce] Carsten Sievers,[abe] Andreas S. Bommarius[abe]

[a.] *School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, 311 Ferst Dr. NW, Atlanta, GA 30332, USA*
[b.] *Renewable Bioproducts Institute, Georgia Institute of Technology, 500 10th St. NW, Atlanta, GA 30332, USA*
[c.] *School of Chemistry and Biochemistry, Georgia Institute of Technology, 901 Atlantic Dr NW, Atlanta, GA 30332*
[d.] *George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, 801 Ferst Dr., Atlanta, GA 30332, USA*
[e.] *Center for a Renewables-based Economy from WOOD (ReWOOD), 500 10th St. NW, Atlanta, GA 30332, USA)*

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1. RME and PMI Calculations

RME was defined as the actual mass of product obtained divided by the total mass of reactants used. PMI was defined as the total mass of all materials (including solvents, additives, etc.) divided by the actual mass of product obtained.

Example Calculation of RME and PMI

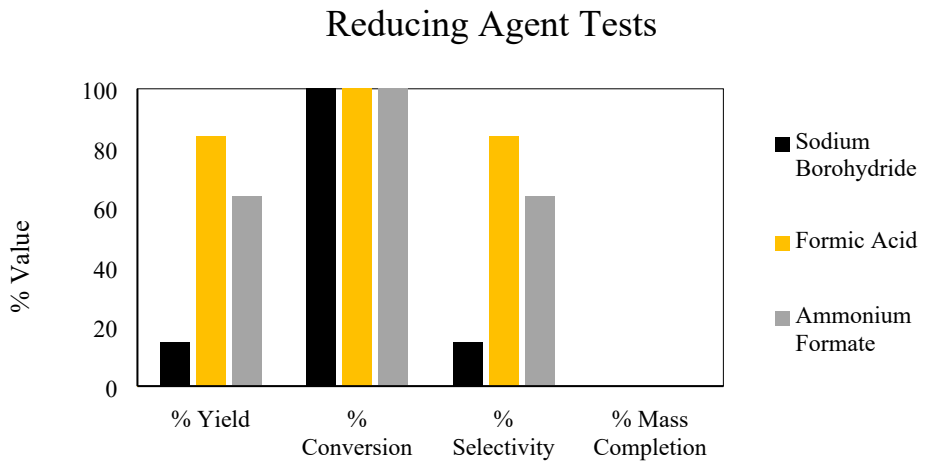
This calculation is for the optimized one-pot bubbler condition.

1 mmol (142.9 mg) 4-nitrophenol, 0.5 mL (393 mg) isopropanol, and 25 mg 5 wt% Pd/C were added to a grinding jar. The reaction vessel was connected to gas tubing and the acetic anhydride bubbler and reacted at 20 Hz for 30 min under 60 SCCM hydrogen flow at 1 atm (160.2 mg hydrogen). The bubbler was massed before and after the reaction, with 206 mg acetic anhydride delivered to the reactor over the reaction time. The mass of paracetamol out was quantified to be 140.7 mg. Catalyst mass was excluded from calculations. Thus, the final calculations are:

$$RME = \frac{140.7}{142.9 + 160.2 + 206} = 0.276$$

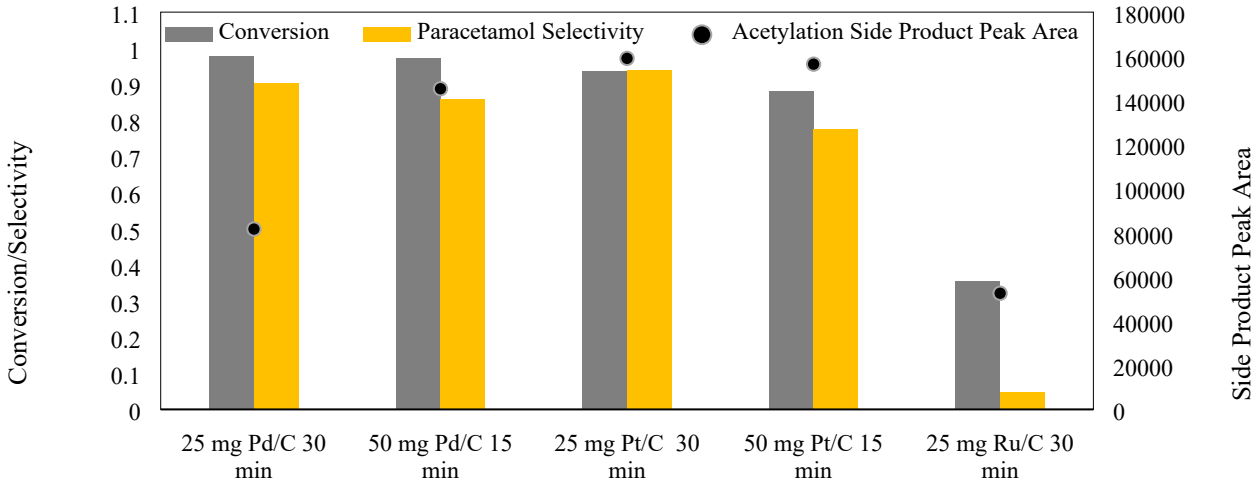
$$PMI = \frac{393 + 206 + 160.2 + 142.9}{140.7} = 6.40$$

2. Transfer Hydrogenating Agent Screen



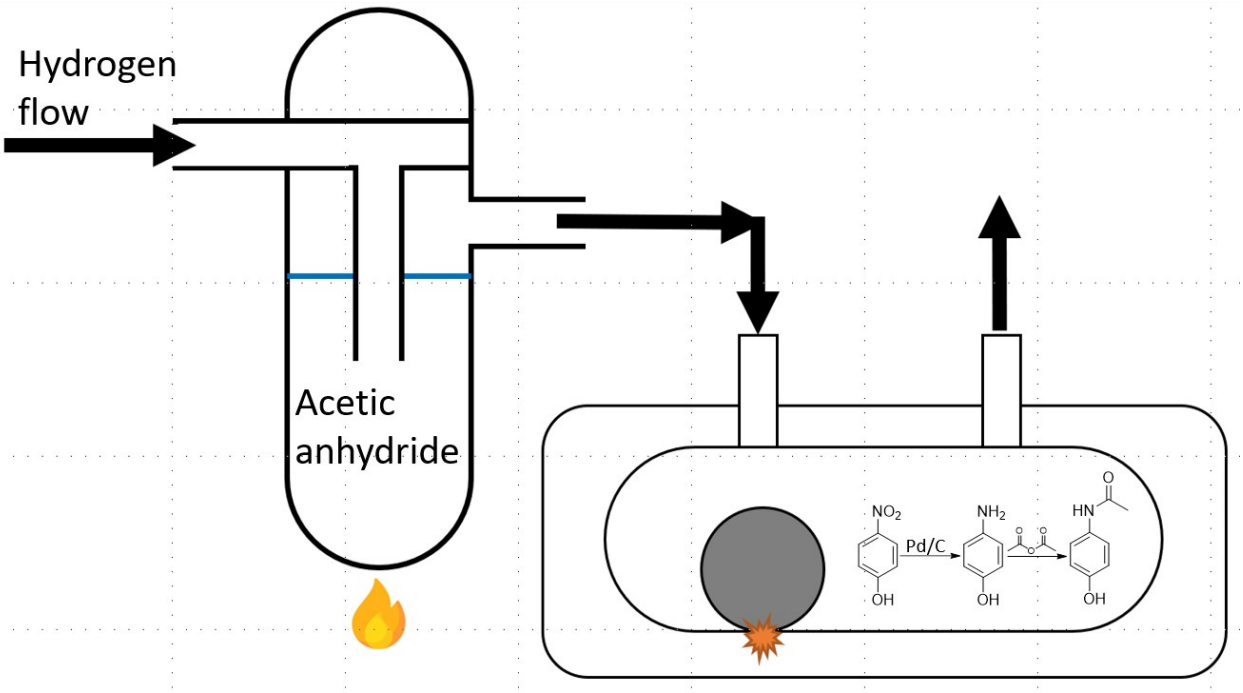
SI Figure 1. 1 mmol 4-nitrophenol was milled with 6.6 hydrogen equivalents of reducing agent at 30 Hz for 30 minutes with 50 mg 5 wt% Pd/C.

3. Catalyst Screen



SI Figure 2. 1 mmol 4-nitrophenol was milled with 2.2 equ acetic anhydride, 0.5 ml isopropanol, and the relevant amount and type of catalyst (5 wt% Pd, Pt, or Ru on carbon) at 20 Hz for 30 min.

4. Ball Mill Reactor Bubbler Setup



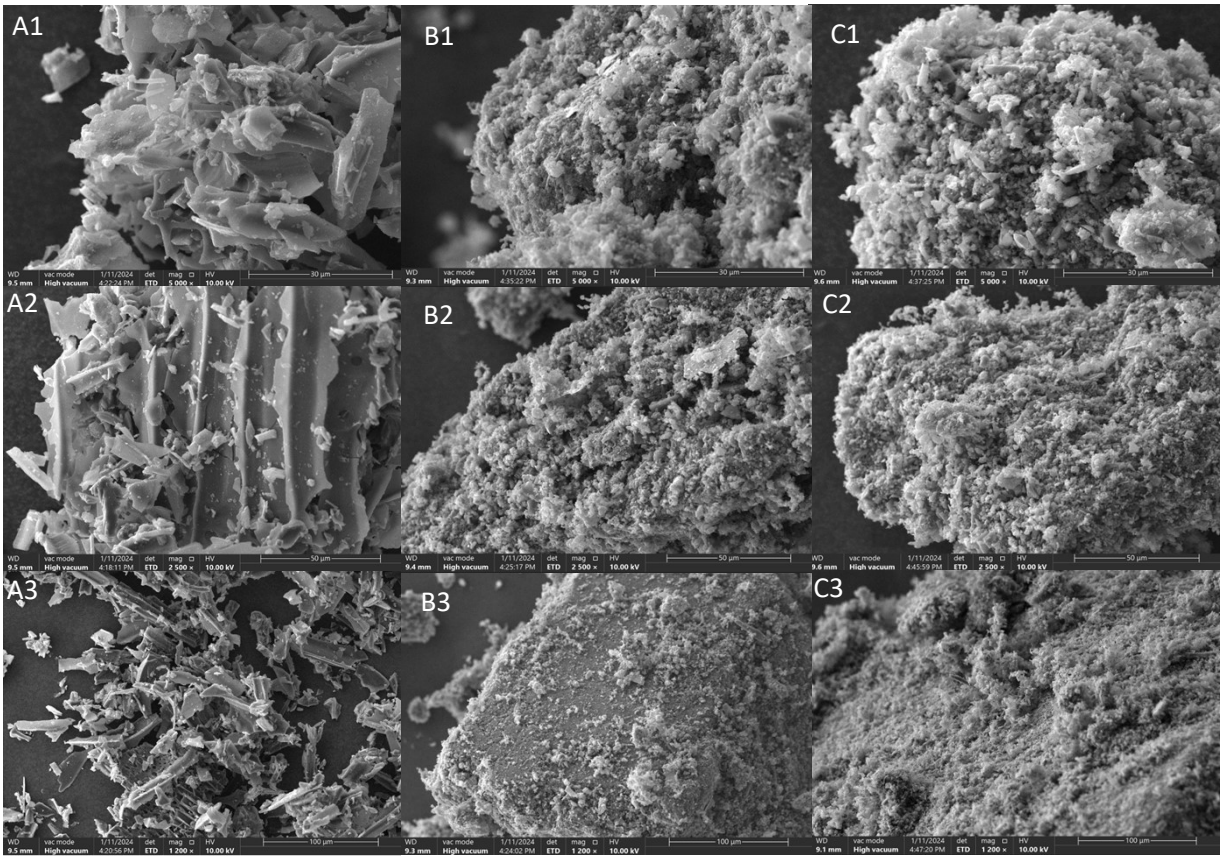
SI Figure 3. Hydrogen was flowed through a bubbler containing acetic anhydride heated to its boiling point with a heated stir plate and oil bath. The hydrogen flow rate was controlled using a Cole-Parmer Mass Flow Controller. Temperature was monitored with a Type K thermocouple. All lines were purged before and after each reaction with nitrogen. Lines were heated to prevent condensation.

5. Catalyst Recycle Procedure

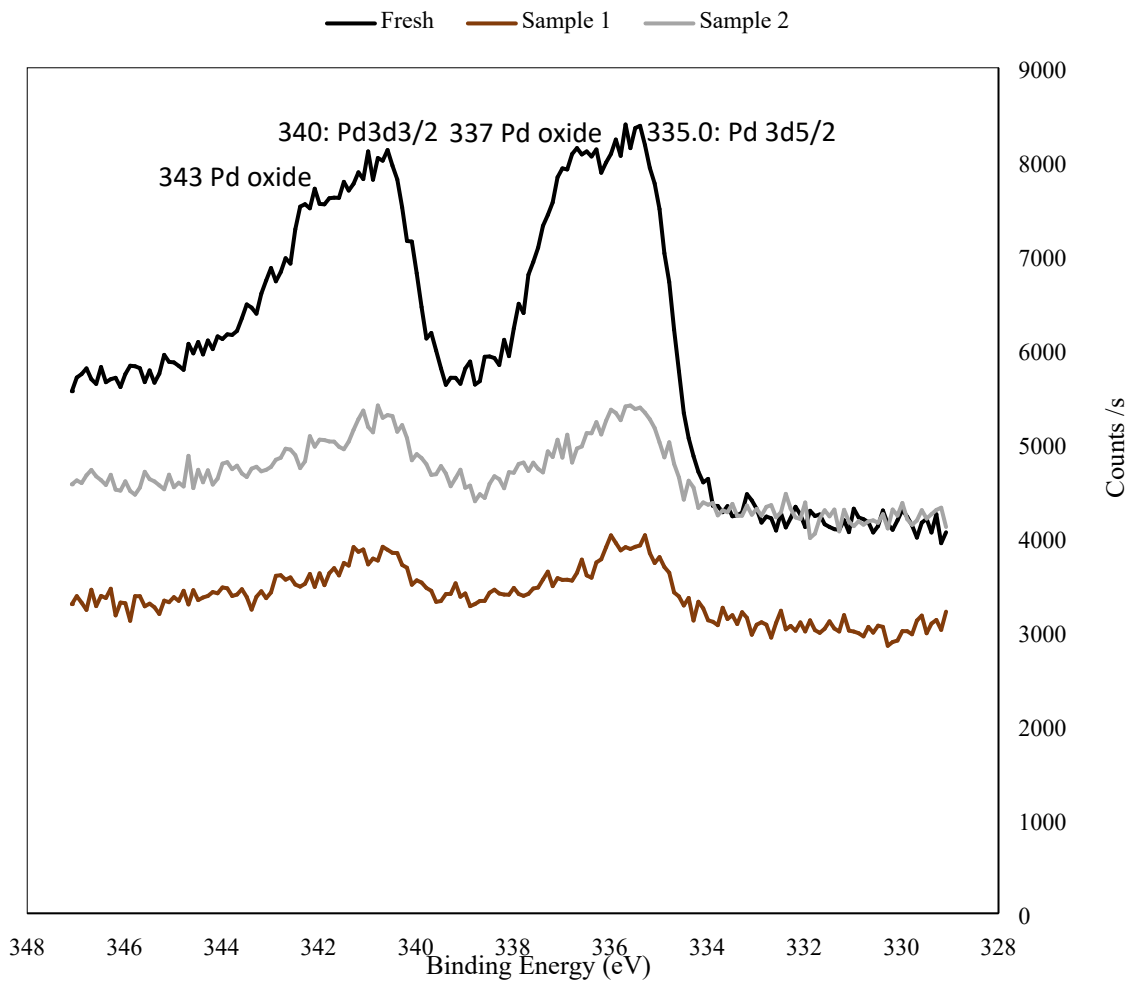
Catalyst recyclability reactions were conducted through direct addition of fresh reactants to the ball mill reactor under hydrogen atmosphere. Originally, the reaction was conducted with 1 27g steel ball at 20 Hz. The recyclability of the catalyst suffered under these conditions, and thus more mild milling conditions were used for subsequent recyclability studies (27 1g steel balls, 15 Hz).

For the first cycle, 70 mg 4-NP, 25 mg 5 wt% Pd/C, and 0.25 ml isopropanol were milled at 15 Hz for 30 min with 27x 1 g steel balls under 60 SCCM hydrogen flow through a bubbler containing acetic anhydride vapor. Afterwards, the reaction vessel was purged with nitrogen and the outlet port opened with nitrogen still flowing (20 SCCM). To the outlet port, 70 mg 4-NP and 0.1 ml isopropanol (to account for evaporation and prevent caking) were added. The outlet port was reconnected to the gas exhaust, the vessel purged 15 min with hydrogen, and milled under the same conditions as the first cycle with no further addition or regeneration of catalyst.

6. Catalyst Characterization



SI Figure 4. SEM images of the catalyst before milling (A1-A3), after harsh milling (B1-B3, 20 Hz, 1x 27 g steel ball), and after mild milling (C1-C3, 15 Hz, 27x 1 g steel balls). Milling was conducted with 50 mg Pd/C 5 wt% under 60 SCCM hydrogen flow for 30 minutes with 0.5 ml isopropanol.



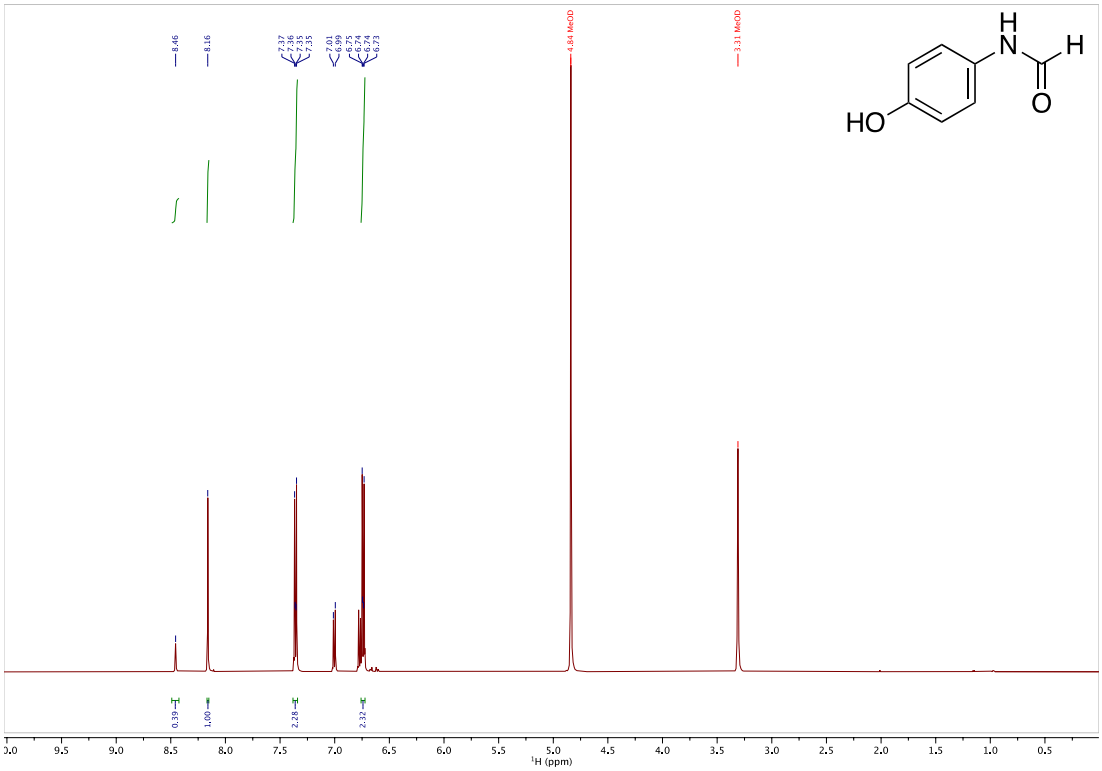
SI Figure 5. XPS spectra of surface Pd species on the catalyst before milling (fresh), after harsh milling (Sample 1, 20 Hz, 1x 27 g steel ball), and after mild milling (Sample 2, 15 Hz, 27x 1 g steel balls). Milling was conducted with 50 mg Pd/C 5 wt% under 60 SCCM hydrogen flow for 30 minutes with 0.5 ml isopropanol.

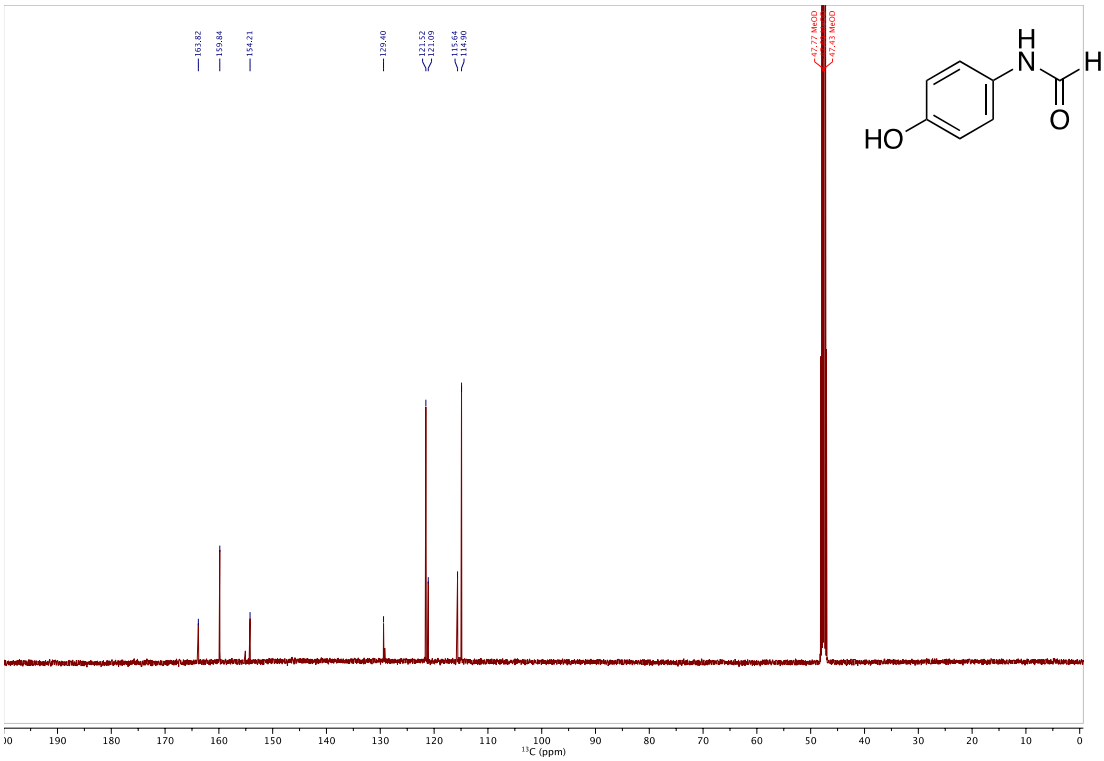
Sample	C/mol%	Pd/mol%	O/mol%
fresh	89.4	1.5	9.1
1	92.0	0.3	7.8
2	93.6	0.9	5.5

SI Table 1. Elemental composition of catalyst surface obtained with XPS before milling (fresh), after harsh milling (Sample 1, 20 Hz, 1x 27 g steel ball), and after mild milling (Sample 2, 15 Hz, 27x 1 g steel balls). Milling was conducted with 50 mg Pd/C 5 wt% under 60 SCCM hydrogen flow for 30 minutes with 0.5 ml isopropanol. Elemental compositions were calculated from averages of scans of three different locations on the catalyst surface.

7. NMR and MS Characterization

4-N-hydroxyphenyl formamide



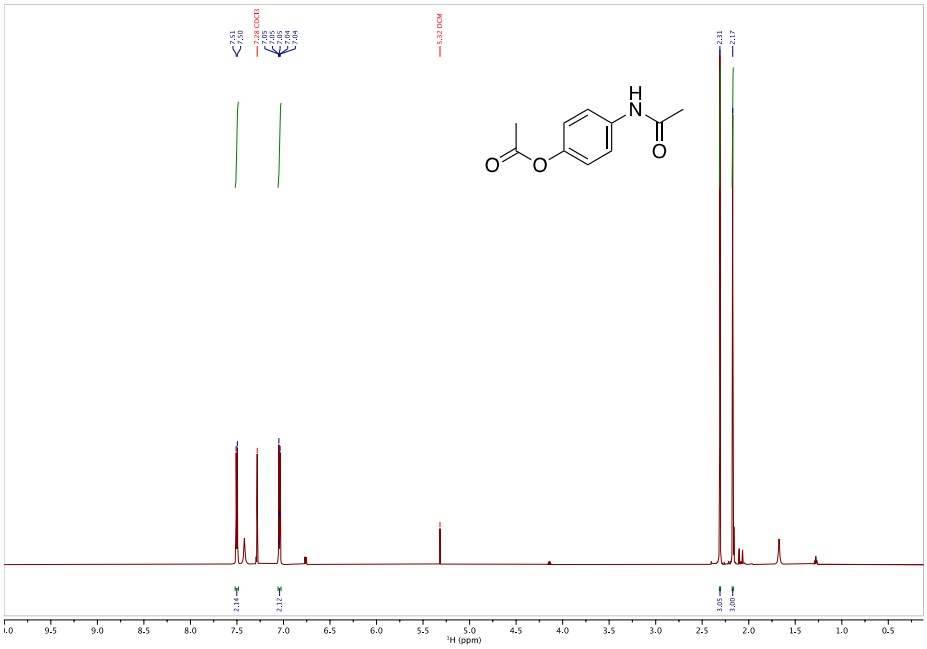


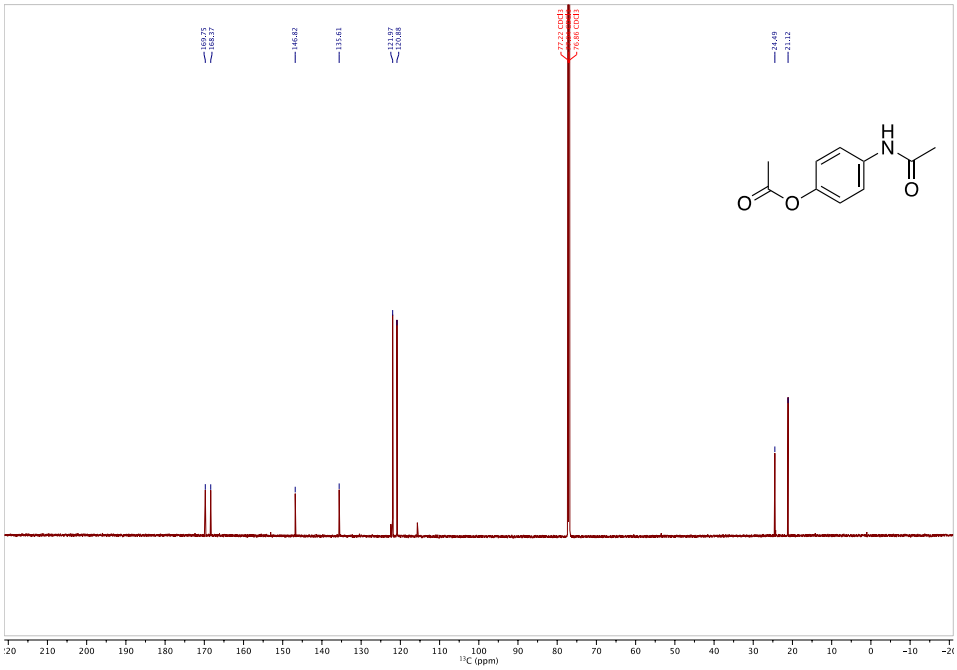
4-acetamidophenyl acetate

MS-ESI (positive mode): [M + H]+, *m/z* = 194.2

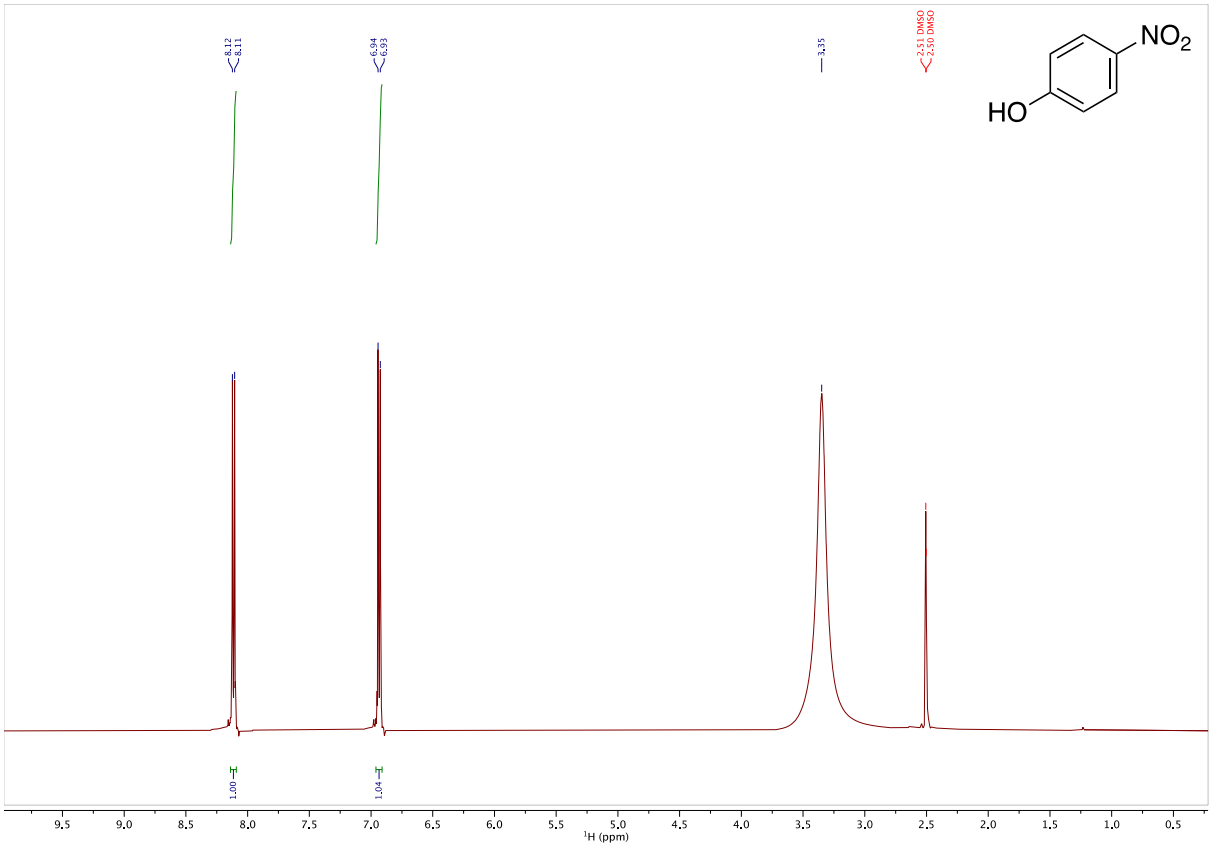
MS-ESI (negative mode): [M – H]-, *m/z* = 195.1

$C_{10}H_{11}NO_3$: Calculated mass 193.21

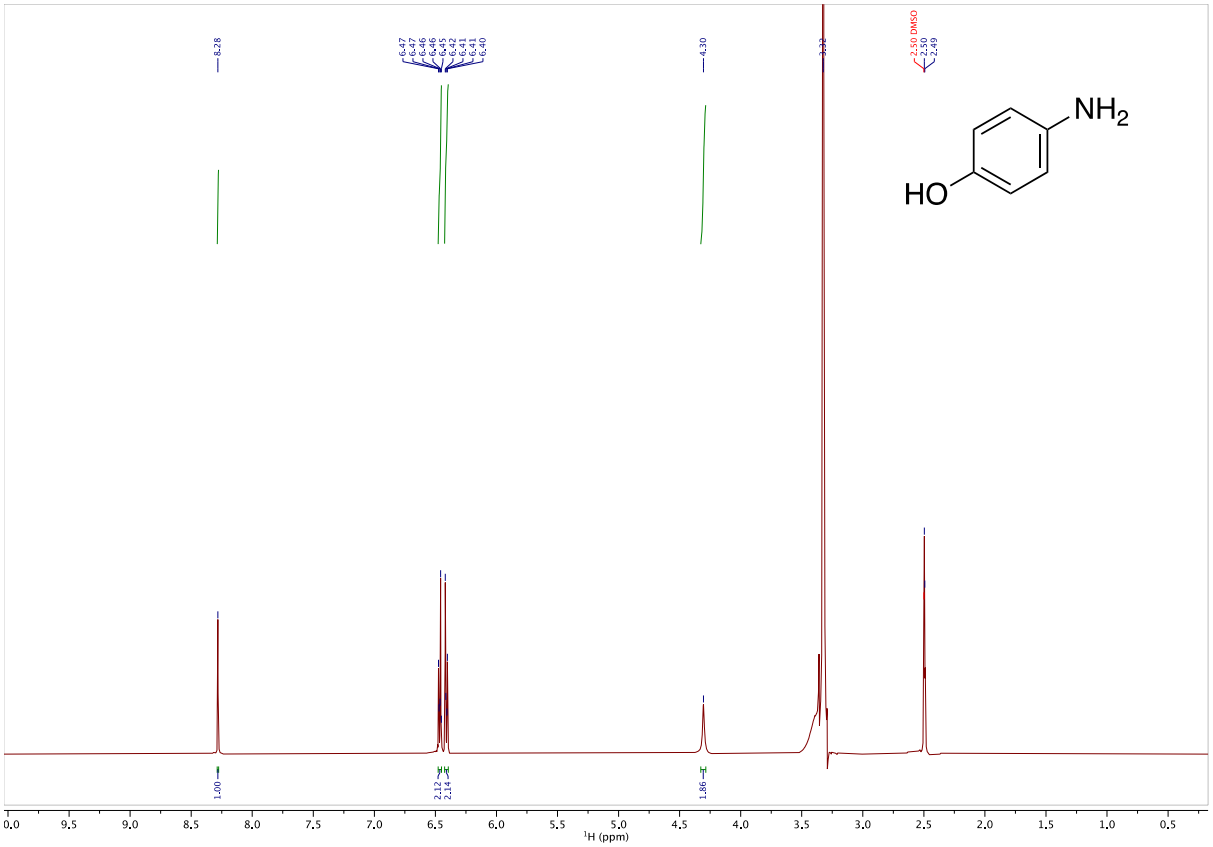




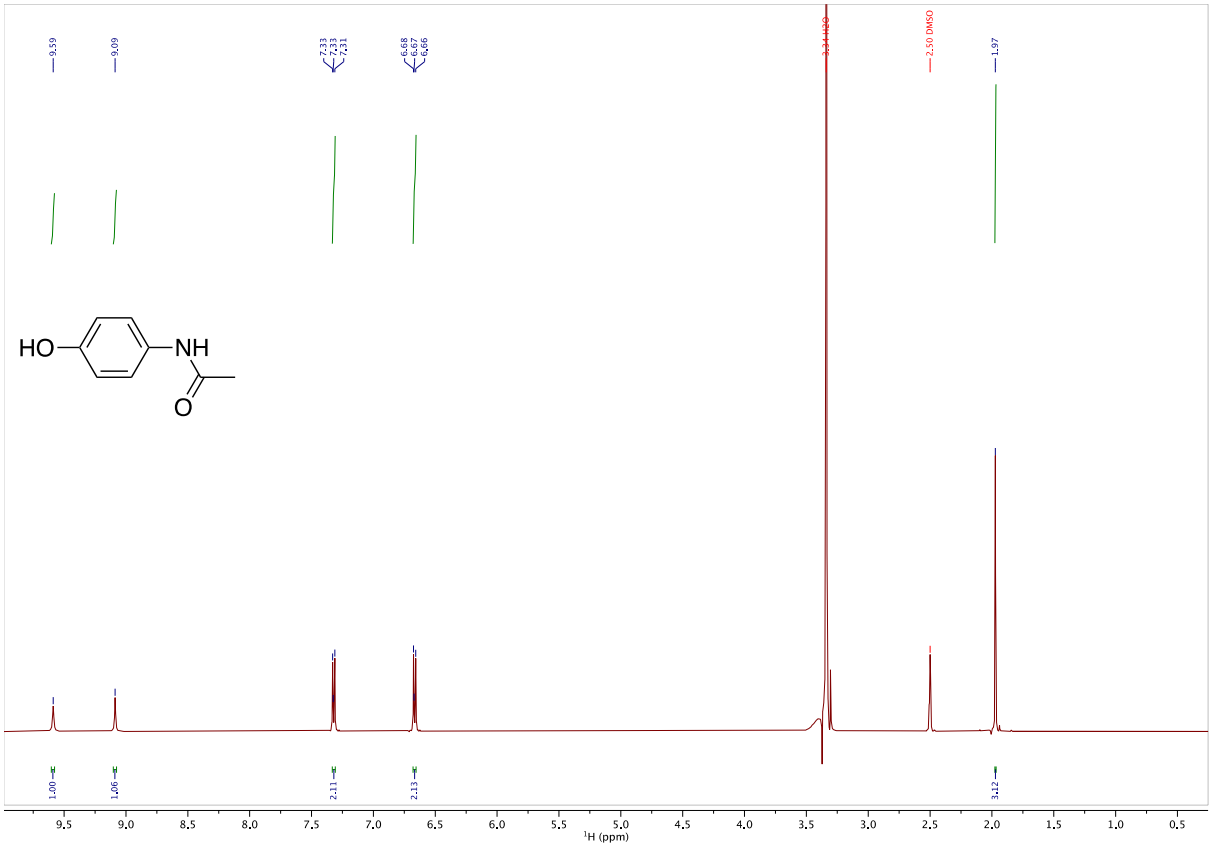
4-nitrophenol



4-aminophenol



Paracetamol



Trimer (4, 4’ – [(2-amino-5hydroxy-2, 5-cyclohexadiene-1, 4-diylidene) dinitrolo] bis-phenol

(CAS 71082-02-5)

MS-ESI (positive mode): [M + H]+, *m/z* = 322.1

MS-ESI (negative mode): [M – H]-, *m/z* = 320.1

$C_{18}H_{15}N_3O_3$: Calculated mass 321.11