

The Art of Heterogeneous Catalytic Hydrogenation Part 1

An Introduction:
Chemistry 536

by Bill Boulanger
Adjunct Professor, Department of Chemistry
University of Illinois at Urbana-Champaign
wboulang@illinois.edu

Recommended Books:

- *Heterogeneous Catalysis for the Synthetic Chemist*
 - Robert L Augustine (1996)
- *Practical Catalytic Hydrogenation, Techniques and Applications*
 - Morris Freifelder 1971

Recommended References

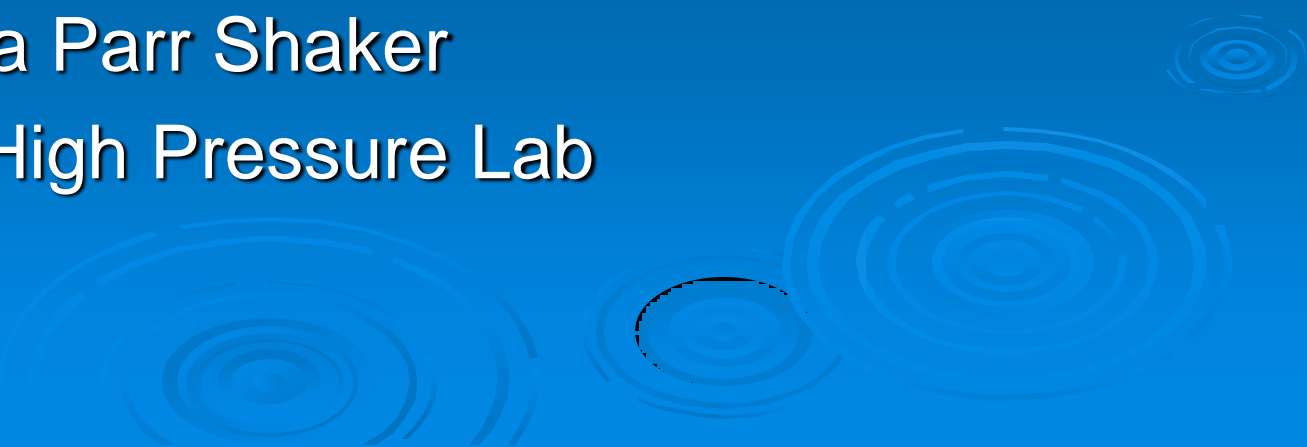
- Catalytic Hydrogenation over Platinum Metals
 - P. N. Rylander 1967

What will Not be Covered Here: (Topics for Another Class)

- Homogenous catalysts
- Chiral catalysis

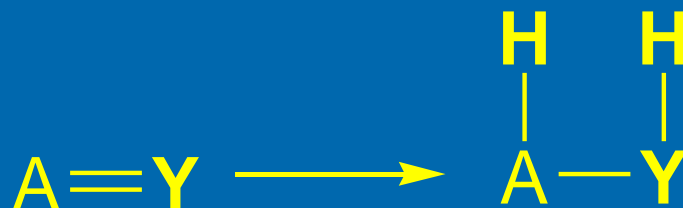


What will be Covered Here:

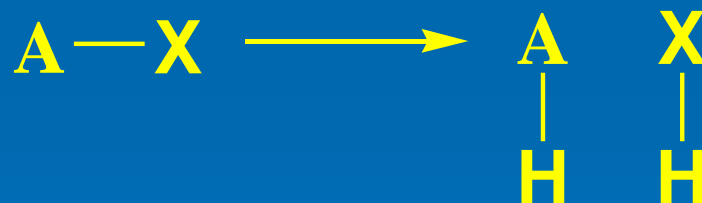
- Some basic theory
 - Catalysts
 - Solvents, and their effects
 - Structure effects
 - Temperature effects
 - Common and useful reductions with hydrogen
 - How to use a Parr Shaker
 - Tour of the High Pressure Lab
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Two Ways to Add Hydrogen:

- Hydrogenation:
addition across Pi
bonds



- Hydrogenolysis:
Cleavage of Sigma
bonds



Catalysts: Overview

- Discrimination dependent upon:
 - Metal
 - Support
 - Solvent
 - Temperature
 - Presence or absence of poisons
 - Promoters

Catalysts Overview, cont'd:

- Rate of reduction dependent upon:
 - Catalyst preparation
 - Time (in hours) since prep. of catalyst
 - Pressure
 - Temperature
 - Loading of catalyst

Why Choose Catalytic Hydrogenation?

- Simple work-up
- Generally clean reactions
- No extra ions or compounds to deal with; just remove solvent.
- Can be done neat.
- Most cost-effective choice for scale-up
- In Process; spent catalyst is usually recoverable for cost savings

Rhenium

- Usually used in an oxide form (recovered in an oxide form)
- Requires vigorous conditions
- Best use is in reduction of carboxylic acids to alcohols or amides to amines
- Typical conditions: 200 atm and 150-250 °C

Ruthenium

- Used as dioxide or metal on support
- Commercially available
- Active at 70-80 °C/ 60-70 atm
- Very resistant to poisoning
- Good choice for reduction of aromatic rings, but does not discriminate.
- Reduces COOH, but only at HP; 500-950 atm.
- Reduces aldehydes, ketones, even sugars.

Copper Chromium Oxide

- Commercially available
- Useful only at elevated temperatures and pressures (250-300 °C/250-300 atm)
- Used for reduction of aldehydes and ketones w/o hydrogenolysis
- No effect on benzene ring
- Used for reduction of amides to amines and esters to alcohols, but now replaced with LAH

Cobalt

- Mostly used in “Raney” form
- Active primarily at elevated pressures and temperatures
- Converts nitriles to primary amines (absence of ammonia)
- Can reduce double bonds and carbonyls at 1 atm, but much less active than Raney Nickel

Just what are Raney metals?

- An alloy of the metal and aluminum is made by melting them together a certain proportions.
- The aluminum is dissolved away using sodium hydroxide solution
- The remaining metal from the alloy “domains” become particles with high surface area and are charged with hydrogen
- It is extremely flammable in air and must be handled wet with water
- Commercially available, but best if prepared just before use. (See Freifelder, p. 7)

Nickel

- Mostly used as Raney Nickel
- Very subject to loss of activity within two weeks of preparation, especially W-6 and W-7
- Only modest temperatures and pressures needed
- Can selectively reduce aromatic rings
- Above 100 °C reaction may get out of hand
- Reduces esters, ketones, nitriles

Nickel cont'd

- Other forms are nickel on kieselguhr and form of Urushibara (*Bull. Chem Soc. Jap* **25**, 280 (1952))
- Can be used in acid solution (HOAc) and can give better results than noble metal catalysts (i.e. better discrimination and yields)

Platinum

- Don't use platinum black: highly variable
- Adam's catalyst (PtO_2)(Stable in storage!) and platinum on support are most common forms; all commercially available
- Wide variety of reductions, including hydrogenation and hydrogenolysis, depending upon conditions; most are mild
- Poisoned by amines and sulfur

Platinum cont'd

- If PtO_2 is pre-treated with HOAc or MeOH wash, can reduce benzene rings readily.
- PtO_2 not selective between double and triple C-C bonds.
- Many variants of Pt/C, each with its own selectivity.

Palladium

- Many forms of palladium on support available, each with its own selectivity
- Less than half the cost of platinum
- Gives both hydrogenation and hydrogenolysis
- Most reductions under mild conditions
- Subject to poisoning with sulfur, amines, and lead.

Rhodium

- Expensive (~Pt), but very versatile.
- Best for reductions of aromatic systems (incl. heterocycles) under mild conditions sans acid
- Reduces C=C, nitro, and carbonyls; most reducible groups
- Aromatic vs carbonyl selectivity can be controlled by pH and nearby groups

Catalyst Inhibitors and Poisons

- Inhibitors diminish the rate , but the effect can be reversed by washing it away.
- Poisons exert an appreciable inhibitory effect when present in small amounts.
- Both can be used to fine-tune the selectivity of a catalyst.

Catalyst Inhibitors and Poisons

➤ Metals and metals Salts

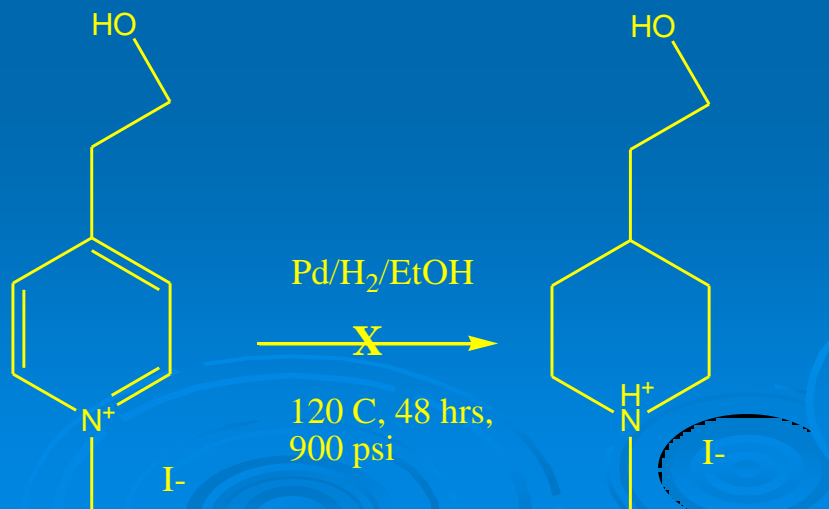
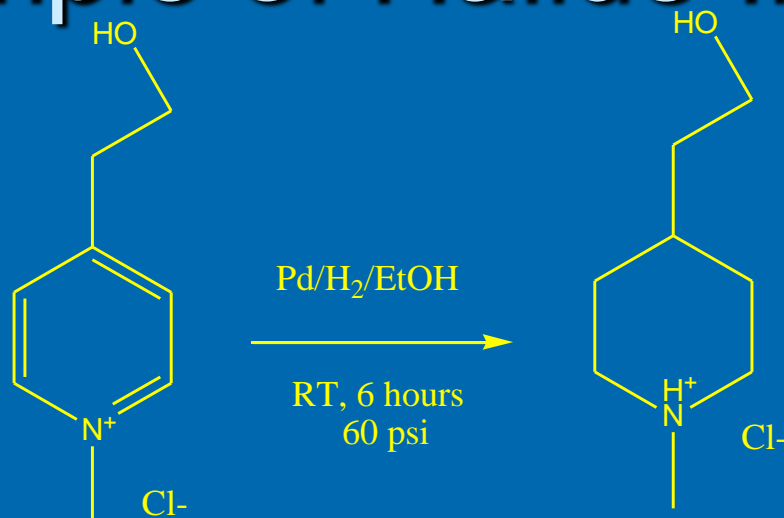
- Mg, Ni Co have no effect on PdCl_2 reductions.
- Al, Fe, Cu, Zn, Ag, Sn, Pb, Hg, Cr their oxides and carbonates inhibit Palladium.
- Pt reductions inhibited by Al, Co, Bi.
- Pt Reductions increased by Fe, Cu Zn, Ag, Pb
- Raney nickel completely inhibited by mercuric chloride, but 50% inhibited by Ag_2SO_4

Catalyst Inhibitors and Poisons

➤ Halogen-Containing Compounds

- Halide ions inhibit Ni, sometimes Pt, Pd: $I^- \gg Br^- > Cl^- > F^-$ in a concentration-dependent manner. Corresponding acids just as potent, if anhydrous. Tip: add water or use acetic acid.
- Non-ionizable organic halides often do not inhibit Pt and Pd, except when directly bonded to the region of reduction (e.g. aromatic halides reduced to cyclohexane halides).
- Potent inhibitors (Ni): carbon tet, chloroform, chloral hydrate, trichloroethanol, di- and trichloroacetic acid, alkyl chloride, benzyl chloride, and acetyl chloride.

An Example of Halide Inhibition



Compounds containing Ar, Sb, O, P, Se, Te

- Oxygen rarely inhibits, except as CO
- Other members of this group are inhibitors if their oxidation state leaves unbonded electron pairs on the central atom.
 - Example: PO_4^{3-} Inert
 PH_3 Inhibitor

Compounds containing Ar, Sb, O, P, Se, Te cont'd

- Sulfate: inert
- Sulfite: Inhibitor
- Phosphite, hypophosphite: inhibitor
- AsH_3 and SbH_3 are poisons, as well as organic derivatives
- Se and Te in lower oxidation states are inhibitors

Sulfur as an Inhibitor

- As sulfides, mercaptans, disulfides, and thiosulfates and thiophenes: potent inhibitors.
- Beware the rubber stopper! Contains sulfur for vulcanizing!
- Some sulfoxides and sulfinates are inhibitors.
- Sulfonates, sulfuric acid, and sulfoxides have little effect.


The Effect of the Nitrogen Atom

- Compounds with unshielded basic Nitrogen act as inhibitors.
- Compounds which generate basic nitrogen on reduction (e.g. nitro, oxime) act as inhibitors.
- Nitrile is an inhibitor (likely due to product), while cyanide is a catalyst poison.
- Non-basic nitrogens (e.g. in amide or urea) have little effect.
- Non-poisonous: Schiff-bases, imines, azines, hydrazones & similar cpds with azomethine links.

Other Nitrogen Inhibitors

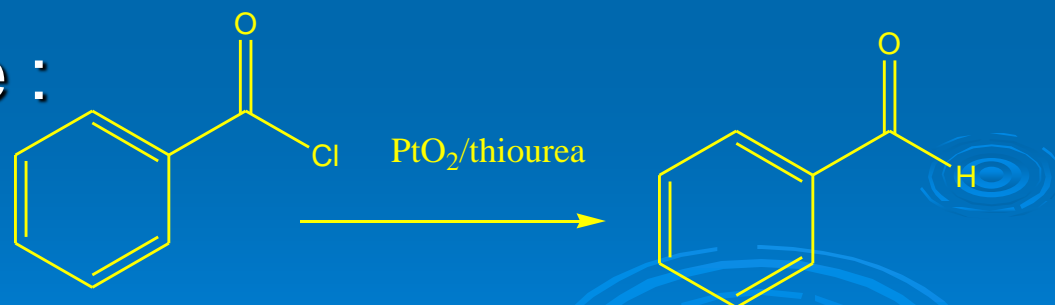
- Pyridine and related heterocycles are inhibitors.
- Piperidine is a potent poison
- Quinoline is only a weak inhibitor, often used for modifying activity

Strategies to Counter the Inhibition by Nitrogen

- Use a protic solvent such as ethanol, methanol
 - Use an organic acid such as acetic acid
 - Use 1 equivalent HCl (less preferable)
 - Choose an alternate catalyst not susceptible to nitrogen inhibition (rarely an option)
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- The bottom right corner of the slide features a decorative graphic of several concentric, light blue circles that resemble ripples on water, set against the dark blue background.

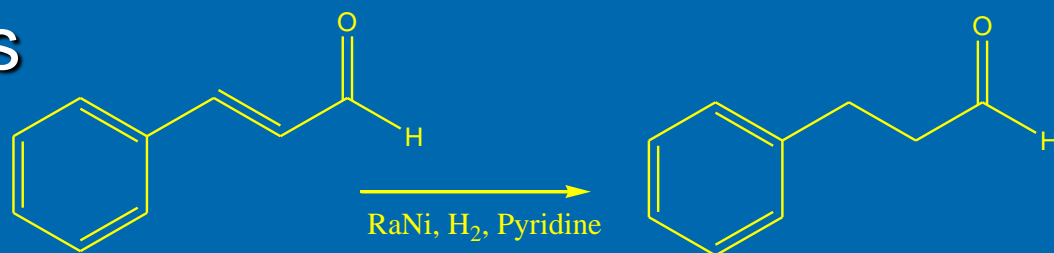
Using Catalyst Poisons

- Effect of poisoning agents not the same for every catalyst
- Can be added to stop a multi-step reduction at a given level of reduction. Example : the Rosamund Reduction:

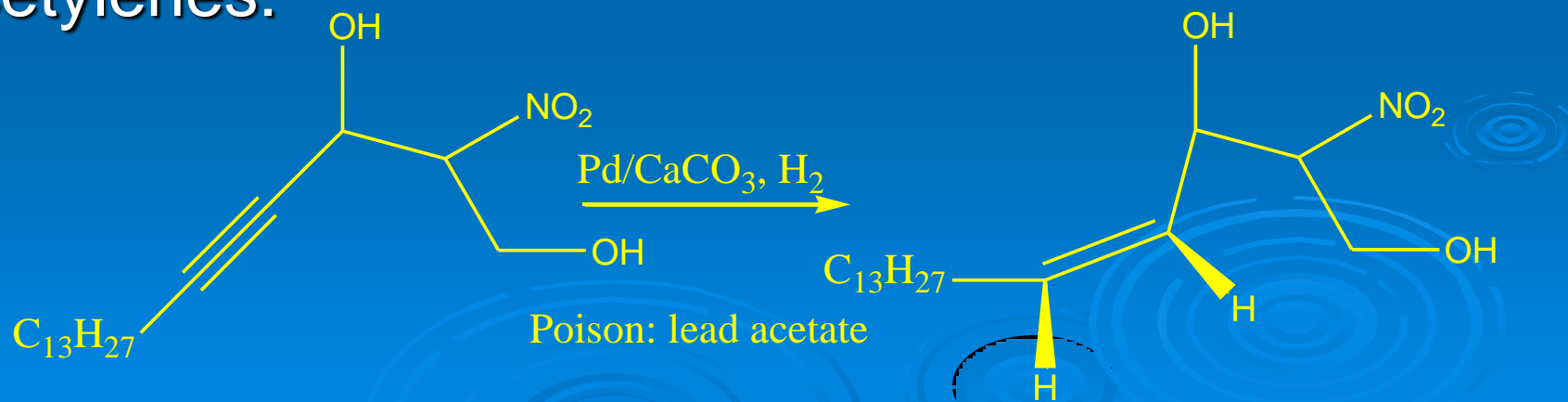


Useful Inhibition

- Reduction of cinnamaldehyde to 3-phenylpropionaldehyde (added pyridine limits reduction):



- Lindlar reduction of acetylenes:

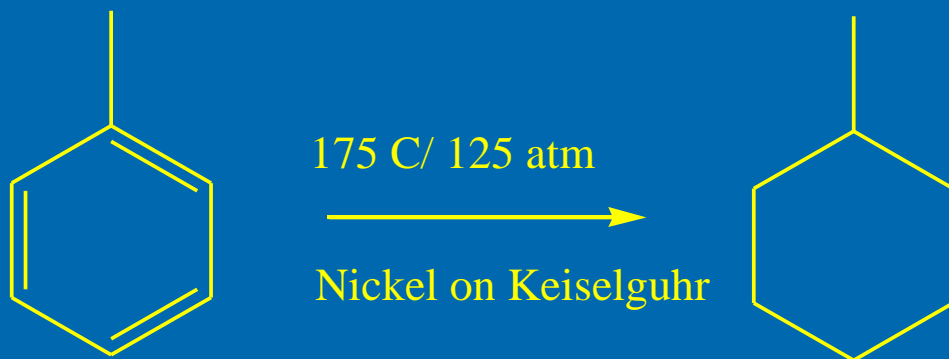


Catalyst Promoters

- Substances that produce greater catalytic effect than can be accounted for by each component independently and in proportion to the amount present
- Most promoters are inactive as catalysts themselves.
- Sometimes are inactivators in another context and/or at a higher concentration
- Promoters tend to be specific to an application.

Examples of promoters:

- Added Cerium distinctly promotes the reduction of toluene:

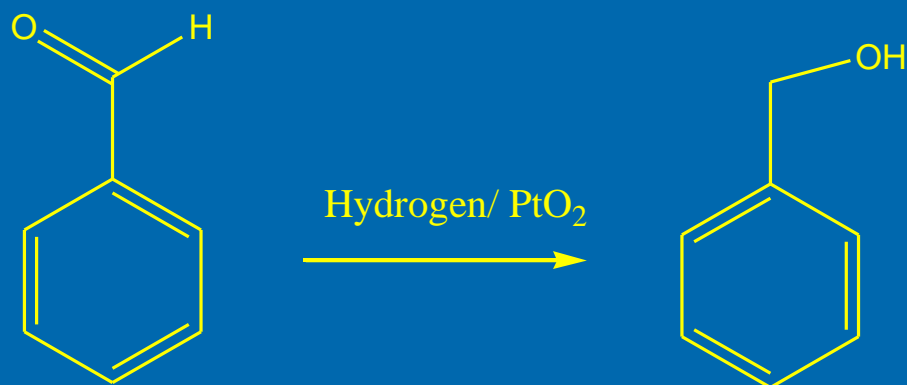


- Addition of 1:1 Mol/mol FeCl_3 to Pt increases rate of reduction of nitro 400%

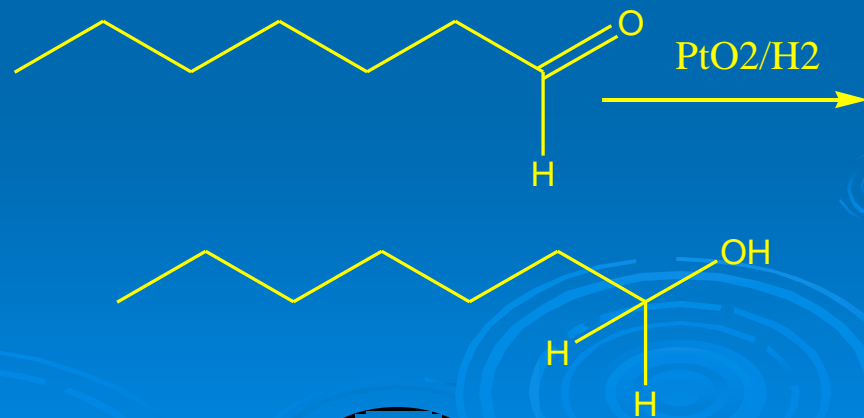


Metal Promoters

- 10 mole% FeCl_3 per g-atom Pt allows reduction of Benzaldehyde at a practical rate:



- SnCl_2 promotes the reduction of heptaldehyde with Pt or PtO₂:



Air as a promoter

- Some reductions, esp. aldehydes over platinum or ruthenium, are very slow if the mixture is not periodically purged with air.
- Need may arise from depletion of “lower oxide” active form of platinum catalyst; purging with nitrogen has no effect.
- Pt/C often has less need. Activated C's contain absorbed oxygen.
- Careful! The procedure involves mixing solvent, air, catalyst to purge residual hydrogen; recipe for an event.

Noble Metals as Promoters of RaNi

- Addition of Pt, Os, Ir, or their salts had a dramatic effect on rate of reduction of a cholesterol ketone; Rh and Ru not effective.
- Most effective as platinum chloride; activates for reductions of nitrile and alkylnitro groups

Basic Promoters

- Addition of KOH or NaOH to Nickel-cat. ketone reductions greatly increases rate. Improved: reduction of nitroanilines, acyl phenols, phenyl phenols, alkyl phenol and free phenols if anhydrous
- Trace Et_3N added to RaNi reductions of aldehydes and ketones cut the time in half. Synergistic with platinum chloride.

Water as a Promoter

- Addition of water most frequently improves ruthenium reductions.
- Ru reductions at low or moderate conditions often do not proceed without presence of water.
- Water counteracts effect of chloride or HCl as inhibitor

Reaction Conditions

- Catalyst
- Adjuvant
- Solvent
- Support
- Loading
- Temperature
- Pressure
- Method of agitation

Solvent

- Hydrogenations can be run sans solvent.
- Solvents moderate reactions and exotherms
- SM does not need to be dissolved or even be significantly soluble, so long as product is.
- Effect of solvent choice is reaction-specific.
- Acidic and basic solvents serve a dual purpose.
- The effect of a neutral solvent is unpredictable.

Solvents continued

- The neoprene stopper of Parr Shakers is attacked by ketones, ethyl acetate, benzene, THF and pyridine, but is inert to alcohols, water, alkane solvents. Solvent choice may require sacrificing stopper or using alternate closure.
- High pressure autoclaves are consistent with any organic solvent *but not mineral acids*.

Solvents continued

➤ Common Solvent Choices:

- Water
- methyl and ethyl alcohol
- Ethyl acetate, cyclohexane, methylcyclohexane, benzene, pet ether, ligroin
- Methyl cellosolve ($\text{MeOCH}_2\text{CH}_2\text{OH}$)
- DMF
- Acetone, MEK

Solvents continued

- Solvents are not always inert:
 - Reduction of pyridine over nickel in lower alkyl solvents results in N-alkylation
 - Reductions in THF and dioxane at high temps over nickel make explosive mixtures. So
 - **DIOXANE AND THF ARE FORBIDDEN IN THE HIGH PRESSURE LAB!**


Support

- Used to increase surface area of catalyst with consequent higher rates
- Modifies Selectivity
- (Process) Minimizes loss of catalyst

Common Supports

- Carbon (many variations): high surface area, absorbs oxygen and impurities; most common and reliable.
- Alumina: Absorbs impurities. pH of Alumina can modulate selectivity.
- Alkaline earth carbonates: impart basicity (in some cases impedes polymerization of alkynes).

Supports

- There are many types of support designed for specific reductions and situations, including
 - Clays
 - Ceramics
 - Pumice
 - Celite
- 

Catalyst Loading

- Rate is semi-proportional to catalyst loading *but not linear*. (Low loading may give no reaction at all, but doubling at midrange may give 5-20x effect).
- Use and report loading based upon weight percent of total catalyst (not contained metal) vs substrate.
- Scale-ups require a smaller loading than pilots.

Table 7.1

Catalyst	Ratio ^a (%)
Copper chromium oxide (copper chromite)	10–20
Palladium, platinum, or rhodium on support	10
Platinum oxide	1–2
Raney nickel	10–20 ^{b, c}
Cobalt ^d	10–20
Ruthenium dioxide	1–2
Ruthenium on supports	10–25

^a The ratio of catalyst to substrate is based on the weight of catalyst not on the percentage of metal to substrate. ^b It is often convenient to measure the volume of wet Raney nickel. When the catalyst has settled, 1 cc is equal to about 1.5 g. ^c Normally a 10% ratio may be sufficient. A larger ratio should be used if the catalyst has been standing for 6 months or more. Dry stabilized nickel catalysts are also available, with which 15–20% weight ratios of catalyst to substrate should be satisfactory. ^d Use in the same manner as nickel with wet or dry catalyst.

Temperature

- Classic rate vs temperature rules apply
- Lower temperatures are preferable, as they exaggerate selectivity differences.
- Many reductions are exothermic; use more solvent, less agitation, or less hydrogen pressure to moderate
- Parr limit: 80°C HP autoclave: 300 °C

Agitation

- Shaking (Parr Shaker) Efficient for small quantities, but difficult to achieve over 2 L.
- Rocking (Rocker autoclaves) Less efficient than rocking or stirring, but best choice for high pressures.
- Stirring: Depending upon design, can be very efficient. Magnetically coupled shafts permit much more reliable performance.
- Extensive discussion in Augustine

Agitation continued

- Rate of reaction increases with efficiency of stirring (e.g. mixing of phases)
- Magnetically stirred microhydrogenators become ineffective above 50 mL.
- Why?



Two Standard Mixers

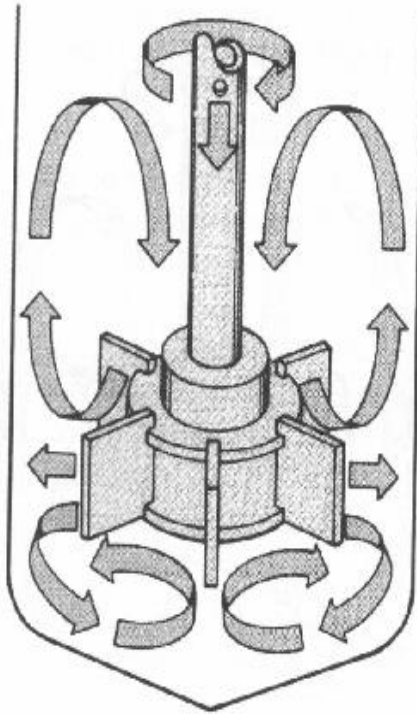


Fig 6.3. Reactor agitation as provided by a six blade Rushton turbine.⁷ Gas dispersion is enhanced by holes in the hollow shaft. (Courtesy Autoclave Engineers.)

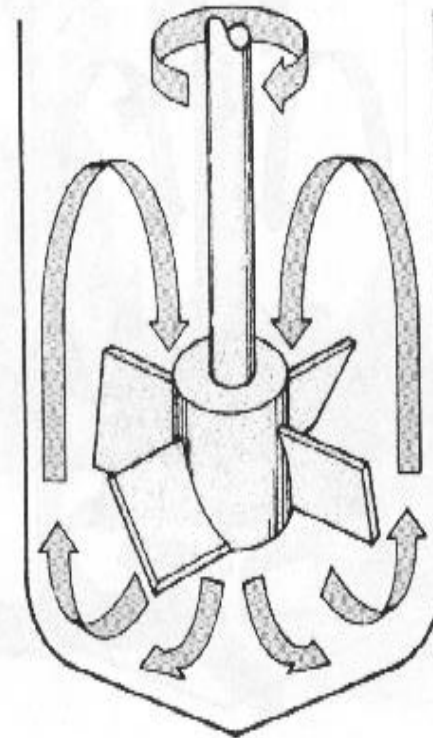


Fig. 6.4. Reactor agitation using a pitched blade turbine. (Courtesy Autoclave Engineers.)

Pressure

- A great many Pt and Pd reductions can be achieved at 60 psi with proper choice of solvent and promoters
- Rate is (nonlinearly) proportional to pressure.
- Some catalysts (Cobalt, copper arsenite) require higher pressures (up to 200 atm) to perform. Some substrates such as aromatics are resistant to hydrogenation and require high pressure

Atmospheric Hydrogenator

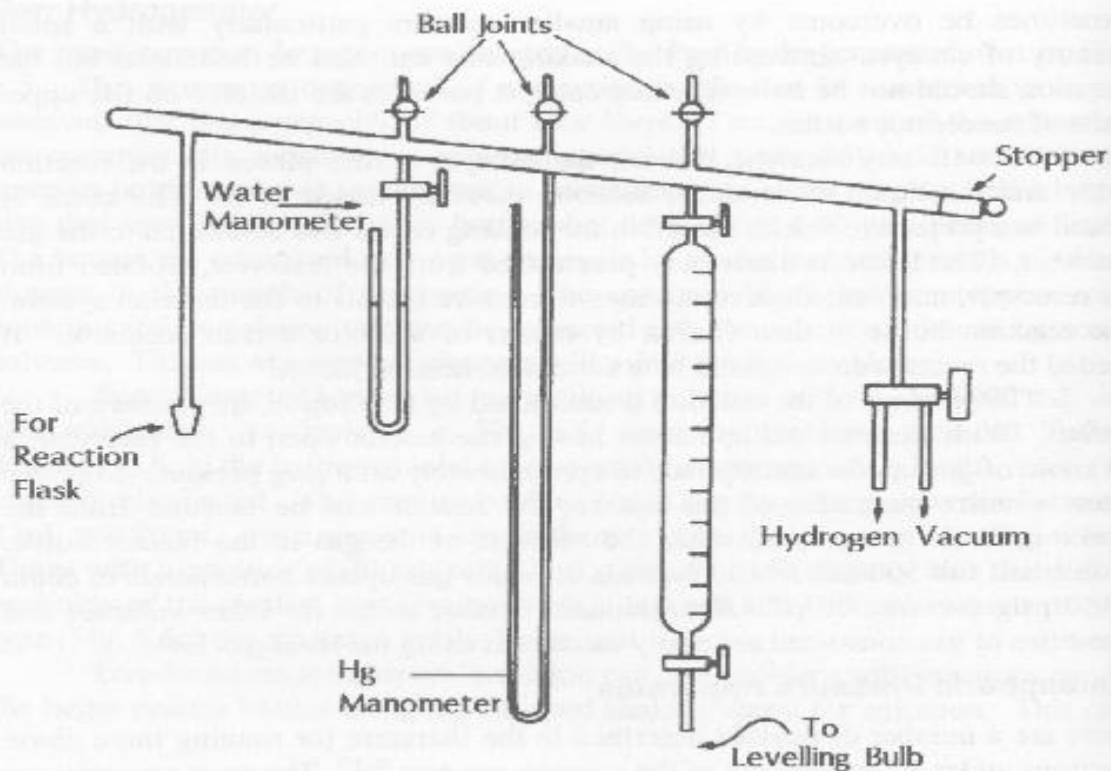


Fig. 6.7. Sloping manifold atmospheric pressure hydrogenator.
(Reproduced, with permission, from Ref. 9.)

End of Hydrogenation Part One

