

### Unit 4: Unit Processes II

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#### 4.1 Reduction: catalytic hydrogenation

Reduction is the mirror image of Unit 3's oxidation and the commonest final bond forming or functional group step in API synthesis: nitro groups to amines, double and triple bonds saturated, benzyl protecting groups removed, carbonyls reduced to alcohols. Its industrial form is **catalytic hydrogenation**, hydrogen gas activated on a metal surface. The elements a process chemist controls:

- **The catalyst.** Palladium on carbon is the general workhorse (alkene and alkyne reduction, hydrogenolysis of benzyl and Cbz protecting groups, nitro reduction). Platinum oxide (Adams catalyst) and platinum on carbon serve acidic media and aromatic ring reductions. Raney nickel, a porous nickel aluminium alloy leached with alkali, is the economical choice for nitrile and nitro reduction and desulfurisation, and is pyrophoric when dry, which dictates its slurry handling. Rhodium and ruthenium catalysts serve aromatic rings and demanding substrates. Lindlar catalyst (palladium poisoned with lead and quinoline) stops alkyne reduction at the cis alkene.
- **The equipment.** Hydrogenation needs pressure rated autoclaves with gas introduction designed for mass transfer (the reaction rate is commonly limited by how fast hydrogen dissolves and reaches the catalyst, so agitation design and gas dispersion are process parameters), hydrogen supply and venting engineered for a flammable gas, catalyst charging under inert conditions, and filtration of pyrophoric spent catalyst kept wet and handled as hazardous waste or sent for metal recovery.
- **Selectivity and its enemies.** Hydrogenation reduces in a rough hierarchy of ease, and chemoselectivity is won by catalyst choice, solvent, temperature, pressure and additives; catalyst poisons (sulfur compounds above all) destroy activity at trace level, so feed purity is a hydrogenation parameter. Partial reductions need poisons used deliberately, as in Lindlar chemistry, or transfer conditions (below).

#### 4.2 Heterogeneous and homogeneous catalysts

| Feature         | Heterogeneous catalysis                                             | Homogeneous catalysis                                                                                                     |
|-----------------|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Form            | Metal on a support (Pd/C, Pt/C, Raney Ni) in a separate solid phase | A soluble metal complex in the same phase as the substrate, for example Wilkinson catalyst, $\text{RhCl}(\text{PPh}_3)_3$ |
| Separation      | Filtration; straightforward, catalyst recoverable                   | Difficult: the metal leaves with the product stream and must be scavenged to meet metal residue limits                    |
| Selectivity     | Broad, robust, sometimes blunt                                      | Finely tunable by ligand design; the basis of asymmetric hydrogenation with chiral ligands                                |
| Operating style | Stirred autoclave, often high pressure                              | Milder conditions possible; sensitive to air and impurities                                                               |
| Cost driver     | Metal loading and recovery from spent catalyst                      | Ligand cost and metal removal                                                                                             |

Homogeneous hydrogenation earns its place because of Wilkinson catalyst chemistry (selective reduction of less hindered double bonds under mild conditions) and because asymmetric hydrogenation, the industrial production of single enantiomers by chiral homogeneous catalysts, is a signature achievement of process chemistry. The heterogeneous default stands on economics and separation: a catalyst you can

filter off is a catalyst you can afford.

## Catalytic hydrogenation: three modes compared

| HETEROGENEOUS                                       | HOMOGENEOUS                                             | TRANSFER                                                 |
|-----------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------|
| Hydrogen gas on a solid metal: Pd/C, Pt/C, Raney Ni | Hydrogen gas with a soluble complex: Wilkinson catalyst | No hydrogen gas: a donor gives the hydrogen instead      |
| Filter off and recover the catalyst                 | Tunable by ligands; asymmetric hydrogenation            | Ammonium formate, cyclohexene, isopropanol               |
| Stirred autoclave, often under pressure             | Metal leaves with product: must be scavenged out        | Ordinary vessels, easy dosing; stoichiometric donor used |

All three put hydrogen onto the substrate at a metal centre

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Figure: Three modes of catalytic hydrogenation: the heterogeneous default, the tunable homogeneous complexes, and transfer hydrogenation without hydrogen gas.

### 4.3 Hydrogen transfer reactions

Transfer hydrogenation avoids gaseous hydrogen altogether: a donor molecule gives up hydrogen to the substrate on a catalyst surface. Standard donors are **cyclohexene and 1,4 cyclohexadiene** (which aromatise to benzene as they donate), **ammonium formate and formic acid** (which decompose to carbon dioxide), **isopropanol** (which becomes acetone, the donor in Meerwein Ponndorf Verley type reductions and in many metal catalysed transfers), and **hydrazine** in specialised cases. The attractions are real: no hydrogen plant, no pressure autoclave, ordinary stirred vessels, easy dosing control, and some selectivities that are hard under hydrogen gas (palladium on carbon with ammonium formate is a standard method for debenzylolation and nitro reduction). The costs are equally real: stoichiometric donor consumption, by product removal, and gas evolution from formate donors that must be vented by design. At commercial scale the balance usually returns to hydrogen gas; transfer hydrogenation dominates at development and smaller scales, which is precisely the judgement the syllabus is training.

### 4.4 Metal hydrides, and the industrial reduction case study

Metal hydride reagents reduce by delivering hydride to carbonyl and related groups, with a reactivity ladder the process chemist must know cold:

- **Sodium borohydride, NaBH<sub>4</sub>:** the mildest common hydride; reduces aldehydes and ketones in protic solvents including water and alcohols; leaves most esters, acids and nitro groups untouched under normal conditions. Cheap, safe to handle as a solid or alkaline solution, and the default first choice at scale.
- **Lithium aluminium hydride, LiAlH<sub>4</sub>:** the strongest common hydride; reduces esters, carboxylic acids, amides and nitriles as well as carbonyls. It reacts violently with water and protic solvents, is handled in ethers, and its work up generates voluminous aluminium hydroxide gels; at scale its cost, hazard and work up burden are arguments for redesign wherever possible.

- **DIBAL H (diisobutylaluminium hydride):** the precision instrument, reducing esters and nitriles to aldehydes at low temperature with one equivalent, in hydrocarbon or ether solution.
- **Borane (BH<sub>3</sub> complexes) and sodium triacetoxyborohydride** fill specialised niches: hydroboration and carboxylic acid reduction for the former, reductive amination for the latter.

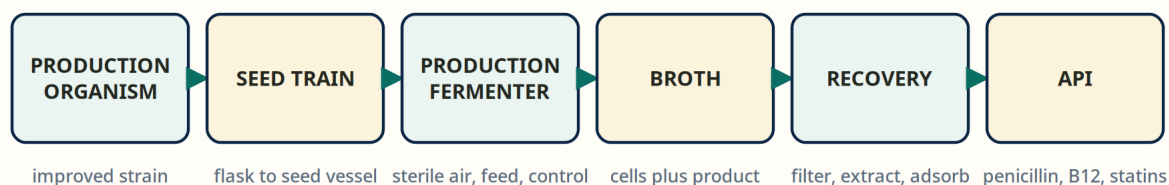
**Case study on industrial reduction**, as the syllabus requests, is taught with the standard example used across the literature: **the reduction of nitrobenzene to aniline**, historically and industrially the largest scale reduction in organic chemistry. The older Bechamp process (iron filings and dilute acid) worked but buried its product in iron oxide sludge; modern manufacture hydrogenates nitrobenzene over metal catalysts, in vapour phase over copper based catalysts or in liquid phase systems, with the exotherm harvested as process steam. The teaching points mirror Section 4.1: catalyst selection for a clean stop at aniline without ring reduction or coupling products, heat removal as the design problem, and waste prevented by choosing catalysis over stoichiometric metal. Every industrial nitro reduction in API synthesis is this case in miniature.

## 4.5 Fermentation: aerobic and anaerobic

Fermentation manufactures molecules that synthesis cannot reach economically, complex natural products built by enzymes in a living cell. The syllabus structure is: aerobic and anaerobic fermentation, then the production of named antibiotics, vitamins and statins.

The process elements are common to all of them. A **production organism** (bacterium or fungus, improved by decades of strain selection and mutation from the original isolate) is grown through a seed train of increasing volumes into a production **fermenter**: a stirred, jacketed, sterilisable vessel with sterile air sparging, agitation, foam control, pH and temperature control and aseptic sampling. **Aerobic fermentation** supplies oxygen continuously, and oxygen transfer is usually the rate limiting engineering problem, addressed by agitation power, sparger design and sometimes enriched air or pressure; penicillin, streptomycin, riboflavin, vitamin B12 and lovastatin production are aerobic. **Anaerobic fermentation** excludes oxygen, the pattern of solvent and acid fermentations and of the first stage of some vitamin B12 processes. **Batch, fed batch and continuous** modes describe feeding: antibiotic and statin processes are typically fed batch, the carbon source fed gradually to avoid catabolite repression and to steer the organism from growth (trophophase) into product formation (idiophase). Contamination control is the existential discipline: a single foreign organism growing faster than the producer ruins the batch, so sterilisation of medium and air and aseptic transfers are validated operations.

## Fermentation: from organism to API



**Aerobic processes: oxygen transfer is the engineering limit**

**Fed batch feeding steers growth into product formation**

*Recovery is designed around the molecule: its stability and its charge*

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Figure: A fermentation process, from the improved production strain to the recovered API; the recovery train is designed around the product molecule.

### 4.6 Production of antibiotics: penicillin and streptomycin

**Penicillin** is the founding industrial fermentation and still the teaching model. The producer is the fungus *Penicillium chrysogenum*, in strains improved by many orders of magnitude over Fleming's isolate. The process is an aerobic fed batch fermentation lasting the better part of a week: a carbohydrate feed (historically lactose, because glucose represses production; modern processes feed glucose at controlled rates) sustains slow growth and then production, and the side chain precursor decides the product, phenylacetic acid feeding giving penicillin G and phenoxyacetic acid giving penicillin V. Temperature, pH and dissolved oxygen are held in narrow bands. Recovery is the unit operations of Unit 2 under time pressure: the broth is filtered to remove mycelium, and penicillin, an acid unstable in water at extremes of pH, is extracted rapidly and cold into a solvent such as butyl acetate at low pH and back extracted into aqueous buffer at near neutral pH, then crystallised as a salt or carried into 6 APA (6 aminopenicillanic acid) production, the platform intermediate for the semisynthetic penicillins.

**Streptomycin** is produced by the filamentous bacterium *Streptomyces griseus*, the actinomycete Waksman's group isolated in 1943, again in aerobic submerged fermentation, typically over several days, on media built from soybean meal and glucose with careful control of pH and aeration. Streptomycin is a basic, water soluble aminoglycoside and stays in the broth; recovery exploits its basicity, by adsorption onto cation exchange resins or activated carbon after broth clarification, elution, and purification to the sulfate salt. The paired examples teach a general rule of fermentation downstream processing: the recovery train is designed around the molecule's stability and charge, acid labile penicillin by fast solvent extraction, base stable streptomycin by ion exchange.

### 4.7 Production of vitamins B2 and B12

**Vitamin B2 (riboflavin)** is manufactured by aerobic fermentation, classically with the fungus *Ashbya gossypii* (and in modern industry also engineered *Bacillus subtilis*), which overproduces riboflavin so strongly that the vitamin crystallises in the broth as its protective response to iron limitation and oxidative stress, turning the culture yellow orange. Vegetable oil or glucose based media, several days of controlled

aeration, and recovery by heat treatment to release and dissolve the vitamin followed by separation and crystallisation give feed and food grade product; the fermentation route displaced a multistep chemical synthesis on cost and waste, a clean example of Section 4.5's economic logic.

**Vitamin B12 (cyanocobalamin)** can only be made at scale by fermentation, because the molecule, a cobalt corrin complex, is far too complex for economical total synthesis. Industrial producers are bacteria such as *Propionibacterium freudenreichii* (run in two stages, an anaerobic phase in which the corrin intermediate accumulates and an aerobic phase in which the final assembly and the dimethylbenzimidazole ligand are completed) and *Pseudomonas denitrificans* (fully aerobic). Cobalt salts are fed because every molecule carries one cobalt atom, and the vitamin is largely inside the cells, so recovery begins with cell harvest and heat or acid treatment to release it, conversion to the stable cyano form with cyanide during work up (hence cyanocobalamin), adsorption purification and crystallisation. The yields are milligrams per litre rather than the grams of penicillin, which is why B12 is the textbook demonstration that fermentation wins not on throughput but on capability.

## 4.8 Production of statins: lovastatin and simvastatin

**Lovastatin** is a fungal secondary metabolite produced by aerobic fermentation of *Aspergillus terreus*, a polyketide assembled by the organism's enzyme machinery. The fermentation is run fed batch over more than a week with tight control of carbon feeding, pH and oxygen, because polyketide production is exquisitely sensitive to nutrient repression; lovastatin accumulates largely in and on the mycelium, and recovery extracts the broth and mycelium with organic solvent and purifies by crystallisation, with the lactone ring opened and closed deliberately during work up because lovastatin is administered as the lactone and acts as the hydroxy acid. **Simvastatin** is lovastatin's close analogue, differing by one methyl group on the ester side chain, and it is manufactured **semisynthetically from lovastatin**: the lovastatin side chain is hydrolysed to the diol intermediate (monacolin J), the lactone hydroxyl is protected, the required 2,2 dimethylbutyrate side chain is esterified on, and deprotection gives simvastatin; modern processes also achieve the key acylation with an engineered enzyme. The pair teach the industry's standard hybrid: fermentation builds the complex skeleton no synthesis can match, and a few chemical steps diversify it into a family of products.

## 4.9 Reaction progress kinetic analysis

Reaction progress kinetic analysis (RPKA), developed and popularised by Donna Blackmond, learns a reaction's kinetics from the progress of the reaction itself, using a handful of experiments rather than a factorial grid of initial rates. Its tools:

- **Reaction progress curves:** concentration against time for the whole course of the reaction, from calorimetry, in situ infrared or sampling. The full curve contains the rate law, catalyst behaviour and inhibition, if read correctly.
- **Graphical rate analysis:** rate plotted against concentration from the progress data; curves from runs at different starting concentrations that overlay share one rate law, and the concentration at which they diverge exposes what differs.
- **Same excess and different excess experiments:** two runs are compared in which the excess of one reagent over the other (for example  $[B]$  minus  $[A]$ ) is the same but absolute concentrations differ; if the progress curves overlay when time adjusted, the catalyst is stable and product does not inhibit; if they separate, product inhibition or catalyst deactivation is diagnosed, and a run with product added at the start distinguishes the two.
- **Orders without initial rates:** running the reaction with different excesses maps the order in each reagent, so a kinetic model is assembled from perhaps three or four experiments.

For the process chemist, RPKA is how a step is understood before it is made big: it finds the true rate determining influences, exposes deactivation a pilot batch would otherwise discover expensively, and defines the addition rates and temperature profiles of Section 1.4 on evidence.

#### 4.10 Streamlining reaction steps and route selection

Route selection applies RPKA style thinking to the whole synthesis. **Streamlining** means removing everything that does not build the molecule: telescoping steps so intermediates are not isolated, deleting protect and deprotect pairs by reordering bond formation, replacing a low yielding step rather than optimising around it, converging the route so expensive material enters late, and choosing the disconnection whose starting materials are commodities. The comparison the syllabus formalises is between the route that is quickest to first material and the route that is cheapest forever.

#### 4.11 Expedient routes and cost effective routes

| Characteristic     | Expedient route                                                    | Cost effective route                                             |
|--------------------|--------------------------------------------------------------------|------------------------------------------------------------------|
| Purpose            | Deliver material fast: for toxicology, trials, first launch supply | Deliver material cheaply and reliably for the product's lifetime |
| Step count         | As found in discovery, modestly tidied                             | Ruthlessly minimised; convergent; telescoped                     |
| Reagents           | Whatever works, including expensive or stoichiometric              | Cheap, catalytic where possible, recoverable                     |
| Starting materials | Catalogue intermediates accepted                                   | Commodity chemicals, dual sourced                                |
| Yield attitude     | Each step good enough                                              | Overall yield optimised, worst step re engineered                |
| Waste attitude     | Acceptable at small scale                                          | E factor and solvent recovery engineered in; waste is cost       |
| Development time   | Weeks                                                              | Months to years, repaid over production life                     |
| Typical flaw       | Cannot be validated economically at volume                         | Late and expensive to develop                                    |

A real programme runs both in sequence: an expedient route supplies development while the cost effective route is built, and the switch between them is itself a project, because changing the route changes the impurity profile and therefore repeats parts of the safety and regulatory argument of Sections 1.8 and 1.9.

#### 4.12 Reagent selection and families of reagents useful for scale up

Reagent selection at scale applies a filter that discovery chemistry never meets: **safety** (thermal stability, gas evolution, toxicity, peroxide formation), **cost and availability at tonne scale**, **stoichiometry** (catalytic beats stoichiometric beats excess), **by product fate** (a reagent whose by product distils out, washes out or can be recycled beats one whose by product must be chromatographed away, there being no chromatography at scale), and **robustness** (sensitivity to water, air and raw material grade). The syllabus phrase "families of reagents useful for scale up" refers to the standard short lists process chemists carry for each transformation, from which a member is chosen on the evidence:

| Transformation | Families carried on the scale up list                                                                                                           |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Bases          | Triethylamine, diisopropylethylamine, pyridine; sodium and potassium carbonate and bicarbonate; sodium hydroxide; DBU for strong hindered cases |

| Transformation                 | Families carried on the scale up list                                                                                                                                                              |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acids (catalytic and work up)  | Hydrochloric, sulfuric, acetic, p toluenesulfonic, methanesulfonic                                                                                                                                 |
| Oxidants                       | Oxygen and air with metal catalysis, hydrogen peroxide systems, sodium hypochlorite (with TEMPO), peracetic systems; classical chromium and manganese reagents reserved and justified case by case |
| Reducing agents                | Hydrogen with Pd, Pt, Ni or Ru catalysts; sodium borohydride; catalytic transfer systems; iron or zinc in acid where catalysis fails                                                               |
| Coupling and activating agents | Thionyl chloride and oxalyl chloride for acid chlorides; carbodiimides at small scale; mixed anhydride and acid chloride methods preferred at scale                                                |
| Solvents as reagents' partners | Water, alcohols, ethyl acetate, toluene, acetonitrile, 2 methyltetrahydrofuran; dipolar aprotics used sparingly and recovered                                                                      |

The habit being taught is substitution by family: when a step specifies a reagent that fails the filter (an expensive coupling reagent, a chromium oxidant, a hydride that gels the work up), the process chemist reaches first within the same family for the member the plant can live with.

#### 4.13 Unit 4 summary

| Item                    | One line essence                                                                                        |
|-------------------------|---------------------------------------------------------------------------------------------------------|
| Catalytic hydrogenation | Hydrogen on a metal surface; rate often set by gas transfer; feed purity is a parameter                 |
| Transfer hydrogenation  | A donor replaces hydrogen gas; simple kit, stoichiometric donor                                         |
| Metal hydrides          | A selectivity ladder from NaBH <sub>4</sub> to LiAlH <sub>4</sub> ; chosen down, not up, where possible |
| Fermentation            | Living synthesis for complex molecules; recovery designed around stability and charge                   |
| RPKA                    | Whole progress curves, same and different excess runs, few experiments, deep knowledge                  |
| Route selection         | Expedient first, cost effective for life; reagent families chosen by the scale up filter                |

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