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MPC202T Advanced Organic Chemistry II, M.Pharm Semester 2

Unit 4: Catalysis: Heterogeneous, Homogeneous, Transition Metal, Organo, Bio and Phase Transfer Catalysis

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4.1 What a catalyst does, and the two great families

A catalyst provides an alternative reaction pathway of lower activation energy. It emerges unchanged at the end, it does not alter the thermodynamics (the equilibrium position is untouched; both directions are accelerated equally), and it is judged by its activity (turnover frequency, molecules converted per active site per unit time), its selectivity (for one product among possible products) and its lifetime. Catalysis is green principle 9: a catalyst replaces stoichiometric reagents and their stoichiometric waste. The syllabus divides the field by phase. A **homogeneous catalyst** is in the same phase as the reactants, usually dissolved in the reaction solvent: every molecule of catalyst is accessible, conditions are mild, the mechanism can be studied and the ligands tuned, but separating the catalyst from the product is difficult and expensive, a serious matter when the catalyst is a precious metal that must not contaminate a drug. A **heterogeneous catalyst** is in a different phase, usually a solid acting on liquid or gas reactants: separation is as simple as filtration, the catalyst is robust and recyclable, and industry loves it, but only surface atoms work, active sites are less uniform, conditions are often harsher, and heat and mass transfer can control the rate.

4.2 Heterogeneous catalysis: preparation and characterisation

A working heterogeneous catalyst is mostly engineering. **Preparation** decides its texture: in impregnation, a support (alumina, silica, activated carbon, a zeolite) is soaked with a solution of the metal salt, dried and then calcined and reduced to the active metal or oxide; in co-precipitation, catalyst and support components are precipitated together for bulk catalysts; ion exchange loads metals into zeolite cages; sol-gel methods build mixed oxides with high surface area. The catalyst that results is described by **characterisation**: the BET method measures total surface area from nitrogen adsorption; chemisorption of hydrogen or carbon monoxide counts exposed metal atoms (metal dispersion and particle size); X-ray diffraction identifies crystalline phases; electron microscopy images the particles; temperature programmed methods probe acidity and reducibility. A supported catalyst is exactly what its name says: small active particles spread over a large area of cheap, strong, porous carrier, so that grams of support carry milligrams of precious metal.

4.3 Heterogeneous catalysis: kinetics, deactivation and regeneration

The kinetic sequence has seven steps: diffusion of reactants through the fluid film to the surface, diffusion into pores, adsorption on active sites, the surface reaction itself, desorption of products, and diffusion back out. The Langmuir-Hinshelwood model, in which both reactants adsorb before reacting, describes many systems and explains their characteristic saturation behaviour: the rate first rises with concentration, then levels off when the surface is full. If diffusion is slow, the observed kinetics describe transport rather than chemistry, and the measured activation energy falls misleadingly, so catalyst testing must prove the surface reaction is rate limiting. Catalysts die by defined mechanisms: **poisoning**, the strong chemisorption of an impurity (sulfur compounds on nickel and platinum are the classic case; lead poisons are why leaded petrol destroyed exhaust catalysts); **fouling or coking**, carbonaceous deposits blocking pores and sites; **sintering**, the thermal migration and coalescence of metal particles into larger, less active ones; and leaching of the active phase into solution. **Regeneration** reverses what is reversible: coke is burned off in

controlled air, poisons are sometimes washed or steamed away, and oxidised metals are re-reduced with hydrogen; sintering is largely irreversible, which is why operating temperature discipline matters.

4.4 Heterogeneous catalysis in the synthesis of drugs

Examples the syllabus asks for are the daily bread of process chemistry:

- **Palladium on carbon hydrogenation** reduces alkenes, alkynes, nitro groups and imines, and cleaves benzyl protecting groups by hydrogenolysis; it appears in the great majority of API routes that contain a reduction step.
- **Raney nickel** performs hydrogenations and desulfurisations (removal of sulfur protecting and directing groups as in the Mozingo reduction) and hydrogenates glucose to sorbitol industrially.
- **Lindlar catalyst** (palladium on calcium carbonate, poisoned with lead acetate and quinoline) stops alkyne hydrogenation at the cis-alkene, a selectivity used in vitamin A and E intermediate manufacture.
- **Adams catalyst (platinum oxide)** reduces under acidic conditions where palladium fails, and platinum and rhodium on supports hydrogenate aromatic rings, as in routes to saturated heterocyclic drugs.
- **Zeolites and solid acids** catalyse alkylations and isomerisations in bulk intermediates manufacture, replacing corrosive liquid acids (green principle 3).

4.5 Homogeneous catalysis and Wilkinson's catalyst

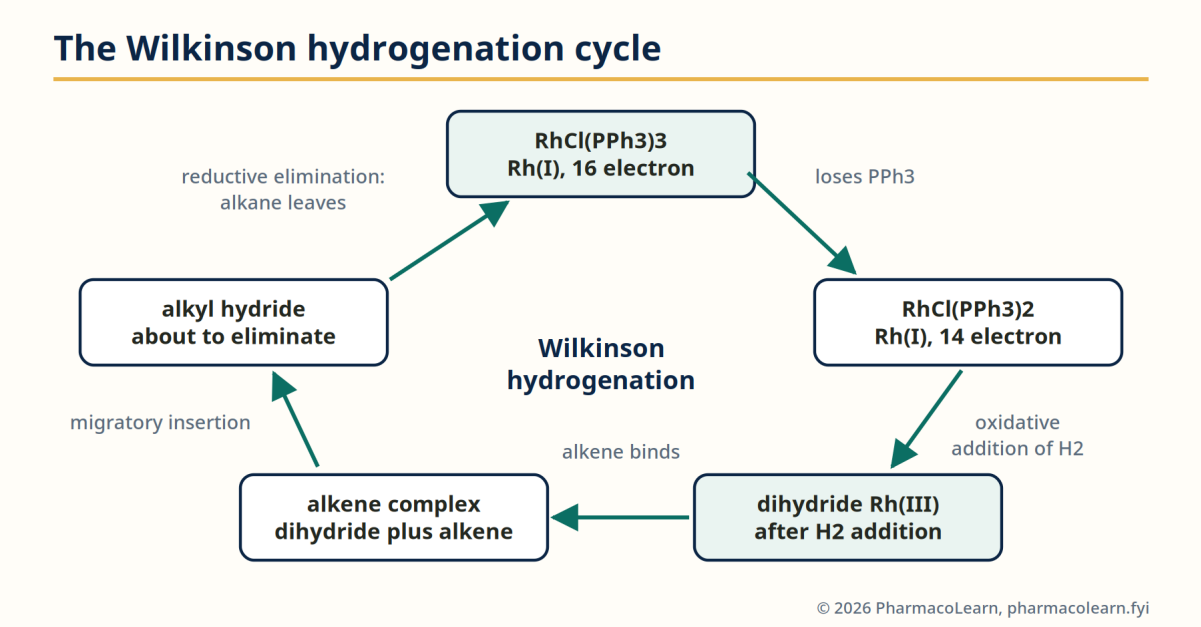

Figure: The Wilkinson cycle: ligand loss, oxidative addition of hydrogen, alkene coordination, migratory insertion and reductive elimination regenerate the catalyst.

Wilkinson's catalyst, chloridotris(triphenylphosphine)rhodium(I), RhCl(PPh3)3, is the teaching model of homogeneous hydrogenation, and its cycle contains every elementary step of the field:

1. The square planar 16 electron complex loses a triphenylphosphine ligand, giving a reactive 14 electron species.
2. **Oxidative addition** of hydrogen gives a rhodium(III) dihydride, the metal rising in oxidation state by two.
3. An alkene coordinates to the vacant site.
4. **Migratory insertion** moves one hydride onto the alkene, forming a rhodium alkyl.

5 **Reductive elimination** joins the alkyl and the remaining hydride and releases the alkane, regenerating the catalyst.

The catalyst's selectivity follows from the mechanism: it hydrogenates the least hindered double bond fastest (terminal before internal, strained double bonds very fast), works at ambient temperature and pressure, and leaves carbonyls, nitro groups, nitriles and benzyl ethers untouched, selectivity no heterogeneous catalyst of its era could match. Its lesson generalises: in homogeneous catalysis the ligand sphere is the design space, and changing the ligands changes the catalyst.

4.6 Hydroformylation and hydrocyanation

Hydroformylation (the oxo process) adds carbon monoxide and hydrogen across an alkene to give an aldehyde one carbon longer. The original cobalt catalyst (HCo(CO)4, formed in situ) required high temperatures and pressures; modern rhodium catalysts with phosphine ligands run far more mildly and give high selectivity for the linear aldehyde, whose alcohol derivatives supply the plasticiser and detergent industries at millions of tonnes per year. Regiochemistry (linear versus branched aldehyde) is controlled by the ligand bite angle and electronics, the clearest large-scale proof that ligands govern outcomes. **Hydrocyanation** adds HCN across a double bond using nickel(0) phosphite catalysts; the DuPont process converts butadiene with two equivalents of HCN into adiponitrile, the nylon-6,6 intermediate, through oxidative addition of HCN, alkene insertion and reductive elimination steps, with Lewis acid promoters steering the second addition to the linear nitrile. Both processes show homogeneous catalysis at its industrial best and its characteristic risk: the metal is dissolved in the product stream and must be recovered completely.

4.7 Chiral ligands and chiral induction

Replace the achiral ligands of a hydrogenation catalyst with a single-enantiomer chiral ligand and the metal complex itself becomes chiral; the two faces of a prochiral substrate now pass through diastereomeric transition states of different energies, and one enantiomer of product forms faster. This is **chiral induction**, and its industrial debut is one of the famous stories of the field: Knowles at Monsanto replaced the triphenylphosphine of Wilkinson's catalyst with a chiral phosphine (DIPAMP) and hydrogenated a dehydro amino acid to **L-DOPA**, the Parkinson's drug, in high enantiomeric excess, the first large-scale asymmetric catalysis. Noyori's Ru-BINAP catalysts hydrogenate beta-keto esters and isomerise allylamines; Takasago uses an Rh-BINAP isomerisation of diethylgeranylamine as the key step of its menthol process. Knowles and Noyori shared the 2001 Nobel Prize with Sharpless for this work. The economic logic is decisive: a few grams of chiral catalyst can manufacture tonnes of single-enantiomer product, which is why catalytic asymmetric synthesis is the third strategy of Unit 5.

4.8 Ziegler-Natta catalysts

The **Ziegler-Natta catalyst**, classically titanium tetrachloride (or TiCl3) activated by triethylaluminium, polymerises ethene and propene at low pressure to linear, high density polymers, and, uniquely in its era, polymerises propene to the **isotactic** form in which every methyl group lies on the same side, giving a crystalline, strong plastic where earlier methods gave a useless sticky atactic gum. The Cossee-Arlman mechanism has the alkene coordinate to a vacant site on titanium and insert into the growing titanium-carbon bond, the surface geometry enforcing the same facial choice at every step. Modern single site metallocene catalysts (such as zirconocenes activated by methylaluminoxane) sharpen the same idea: every active site identical, polymer molecular weight and tacticity precisely controlled. The relevance to this syllabus is twofold: polymer manufacture is the largest-scale catalysis on earth, and isotacticity is stereochemistry written at the scale of thousands of stereocentres per molecule.

4.9 Transition metal and organocatalysis in modern synthesis

Transition metal catalysis beyond hydrogenation is built on the same elementary steps as Wilkinson's cycle: oxidative addition, transmetalation, migratory insertion and reductive elimination. The palladium cross couplings of MPC102T (Suzuki above all) are its flagship, joined by Heck, Sonogashira, Buchwald-Hartwig amination and olefin metathesis (Grubbs catalysts), the reactions with which modern medicinal chemistry assembles drug scaffolds. **Organocatalysis** uses small organic molecules instead of metals: the amino acid (S)-proline catalyses intramolecular aldol reactions through an enamine intermediate (the Hajos-Parrish reaction, known since the 1970s and the spark of the modern field); chiral imidazolidinone catalysts developed by MacMillan activate aldehydes as iminium ions and control Diels-Alder and other cycloadditions; hydrogen bond donor catalysts such as thioureas activate electrophiles by binding. Organocatalysts are robust, non-toxic, metal free (so no metal residue problem in the API) and often derived from the chiral pool; their price is higher loadings, typically 5 to 30 mole percent. List and MacMillan received the 2021 Nobel Prize for asymmetric organocatalysis.

4.10 Biocatalysis: enzymes as catalysts

Enzymes are the most selective catalysts known: operating in water at ambient temperature and near neutral pH, they routinely distinguish enantiomers, regioisomeric positions and similar functional groups in one step. The working classes in synthesis are hydrolases (lipases and esterases for kinetic resolutions and amide formation; penicillin G acylase, which produces 6-APA, the nucleus of the semisynthetic penicillins, industrially), oxidoreductases (ketoreductases making chiral alcohols, transaminases converting ketones to chiral amines), and lyases such as nitrile hydratases. Two examples mark the state of the art: the enzymatic kinetic resolution of racemates with lipases, a standard route to single-enantiomer alcohols and amines, and the **sitagliptin process**, in which an engineered transaminase, evolved in the laboratory to accept a bulky ketone it would never naturally meet, replaced a rhodium-catalysed hydrogenation, raising yield, removing the precious metal and cutting waste in one move. The limitations are real (narrow substrate ranges, product inhibition, enzyme cost, dilute aqueous streams), and protein engineering exists to remove them.

Immobilised enzymes and cells answer the recovery problem the way heterogeneous supports answer it for metals: enzymes are adsorbed on carriers, entrapped in gels such as calcium alginate, covalently bound to supports, or cross-linked into insoluble aggregates (CLEAs); whole cells are immobilised when a multi-enzyme pathway or cofactor recycling is needed. Immobilisation allows packed bed continuous reactors, repeated reuse over many batches, easier product isolation and often better stability to heat, pH and organic solvents.

4.11 Phase transfer catalysis

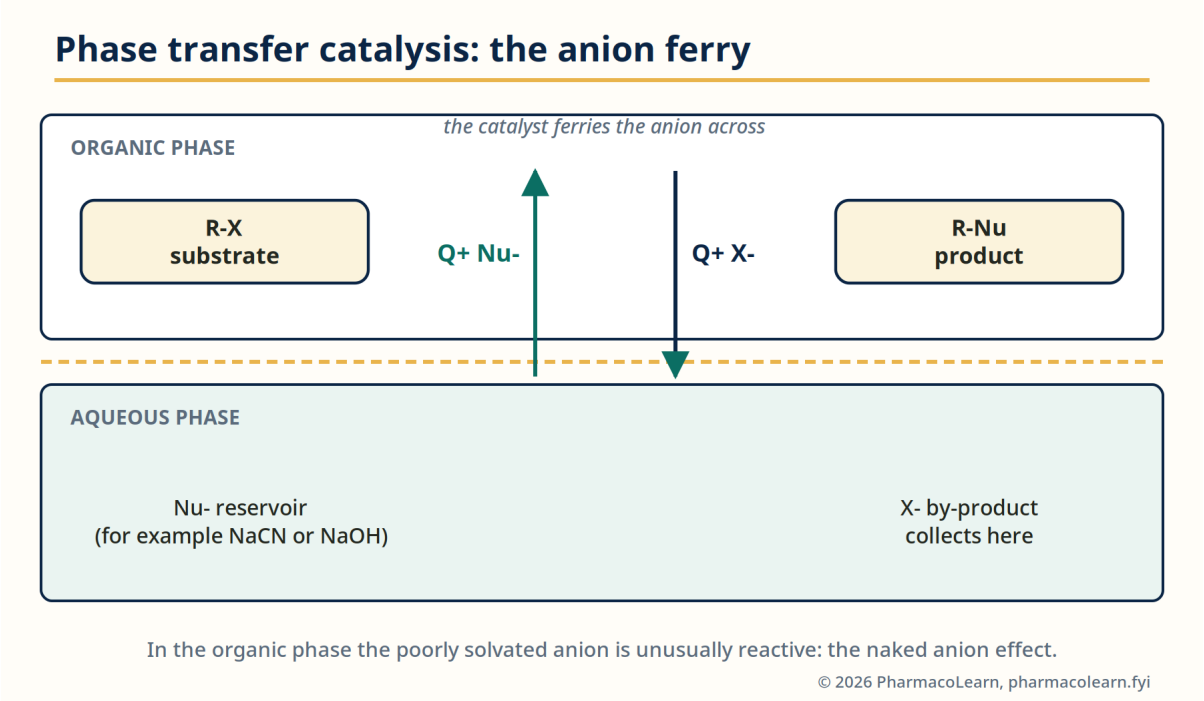

Figure: The quaternary ammonium cation ferries the nucleophile into the organic phase as Q+ Nu- and returns with the leaving anion as Q+ X-.

Many reactions pair a reagent that lives in water (hydroxide, cyanide, permanganate) with a substrate that lives in an organic solvent, and the two never meet. A **phase transfer catalyst** ferries the anion across the boundary. In the Starks extraction picture, a lipophilic quaternary ammonium cation (tetrabutylammonium, or Aliquat 336) exchanges its counterion for the reactant anion in the aqueous phase, carries the ion pair into the organic phase, where the anion, poorly solvated and therefore unusually reactive (a "naked" anion), reacts with the substrate; the catalyst returns with the leaving anion and cycles. Makosza's interfacial picture places the key deprotonation or exchange at the interface itself, important when the catalyst is less lipophilic. Crown ethers do the same job for metal cations (18-crown-6 wraps potassium, making potassium permanganate dissolve in benzene as "purple benzene"), and polyethylene glycols are the budget catalysts. Applications fill the classical repertoire: alkylations of phenols, malonates and nitriles with aqueous alkali and no dry solvents; cyanide and azide displacements; dichlorocarbene generation from chloroform and concentrated sodium hydroxide (Makosza conditions) for dichlorocyclopropanation; the Darzens glycidic ester synthesis; and oxidations by permanganate or hypochlorite in organic media. Phase transfer catalysis is green chemistry in practice: water as a co-solvent, no anhydrous conditions, cheap inorganic bases, and easy work-up.

Property	Homogeneous	Heterogeneous
Active sites	Every molecule, uniform and tunable	Surface atoms only, varied sites
Conditions	Mild, low temperature	Often hotter, more forcing
Selectivity	High, ligand designable	Lower precision, but shape selectivity in zeolites
Separation	Difficult, metal contamination risk in APIs	Filtration, recyclable, suited to continuous flow
Deactivation	Ligand oxidation, metal plating out	Poisoning, coking, sintering
Typical examples	Wilkinson hydrogenation, hydroformylation, cross couplings	Pd/C hydrogenations, Ziegler-Natta polymerisation

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