Toolkit for the study of catalytic reaction mechanisms.

A. Reaction kinetics

Kinetics tells us about the reaction order - the change in molecularity between the resting state and rate-limiting transition state

Potential information obtained:

What is the response of the reacting system to changes in the concentration of each component? I.e. contribution to terms in the rate equation.

How does the reactivity change in response to changes (electronic or steric) in the structure of reactants?

Is there evidence of an induction period? Loss of reactivity through catalyst degradation? Acceleration by additives?
Toolkit for the study of catalytic reaction mechanisms
B. Spectroscopy and structure

NMR
Permits detailed analysis of the structure (and dynamics) of stable states - resting state, reactive intermediates - accurate concentrations. Proton NMR shows full complexity of the system, heteronuclear NMR gives selective information (controlled). Phosphorus and carbon NMR very useful.

X-ray structure
Provides detailed understanding of ground states and reactive intermediates

Electrospray Mass Spectrometry
Samples the solution, and reveals ions or easily ionised components. Defines molecular weights with high precision but is insensitive to concentration.

Infra-red (React-IR)
Rapid in situ measurements provide an easy way to follow the course of a reaction

Circular Dichroism
Useful for following chiroptical changes in asymmetric catalysis.
Challenges; ground (resting) state; transition state (turnover-limiting); true intermediates

If we need to understand a reaction mechanism, here is the ground to cover:

*Full kinetic model, identification of reactive intermediates.*

*Tracking atoms between reactant and product.*

*Variation of reactivity with structure*

*The extent of charge separation as the reaction proceeds*

*Whether the reaction is concerted or stepwise.*

We can employ experimental techniques that probe transition states indirectly, but increasingly their analysis is illuminated by Quantum Chemistry. The combination of DFT and fast computers makes this accessible to all.
The Hammond postulate informs us about the likely structure of transition states

If two states, for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of the molecular structures.

In plain English that means - transition-states for quenching of highly reactive species are close to them in structure and energy.
The Curtin–Hammett Principle applies to all equilibrating systems.

Where fast equilibria exist in a reacting system the proportions of products formed are independent of the equilibrium ratio.

B is more stable than A in their fast equilibrium. In contrast the formation of C is faster than the formation of D. The ratio is only dependent on DDG‡.
The historical basis for analysis of catalytic kinetics lies in the analysis of enzymes by Michaelis and Menten; simplified case presented here.

Scheme 1: Reaction sequence of the simplest case of Michaelis-Menten Kinetics. (E = catalyst, S = substrate, ES = catalyst-substrate complex, P = product, $k_i$ = rate constants)

Fuller derivation at the end of this lecture.
Typical low pressure constant volume hydrogenation kit

During the reaction the pressure changes and so the data needs to be analysed by computer simulation.

Starting pressure ca. 2 atm.
Two step mechanism – substrate binds strongly to the catalyst. Measure $[H_2]$ uptake = [Substrate] depletion

\[
\text{Cat} + \text{Sub} \xrightarrow{k_1} \text{Cat.Sub} \xrightarrow{k_2} \text{Product}
\]

strong binding of substrate to catalyst

Varies as $[S]_0$
Two step mechanism; substrate binds weakly to the catalyst

\[
\text{Cat} + \text{Sub} \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} \text{Cat.Sub} \longrightarrow \text{Cat.Sub} + \text{H}_2 \underset{k_2}{\longrightarrow} \text{Product}
\]

weak binding of substrate to catalyst

\[
[S]/M \rightarrow 1 \\
[S]/M = [S]_0 - [S]
\]

Varies as \([S]^1\)
Real life data for a hydrogenation reaction in two different solvents

\[
\text{Cat.} + \text{Sub} \xrightleftharpoons[k_1, k_{-1}]{??} \text{Cat.Sub} \xrightarrow{H_2, k_2} \text{Product}
\]

In between the extremes
The mechanism of hydrogenation with Wilkinson’s catalyst

$^{31}$P NMR evidence

Reactive intermediates observed by spin excitation transfer; both the diphosphine A and the diphosphine dihydride B are accessible.
The mechanism of hydrogenation with Wilkinson’s catalyst – kinetic evidence

Resting state:

- PPh₃
- Ph₃P
- P₂RhCl
- P₂RhHCl

Products:

- H₂ fast
- rate-determining

Kinetics:
- inverse dependence on [PPh₃]
- dependence on [alkene]
The accepted mechanism for hydrogenation with Wilkinson’s catalyst; dihydride under reaction conditions

**resting state**

\[
\begin{array}{c}
\text{Ph}_3\text{P} \quad \text{Rh} \quad \text{Cl} \\
\text{H} \quad \text{Ph}_3\text{P} \quad \text{Cl} \\
\text{PPh}_3 \\
\text{PPh}_3 \\
\end{array}
\]

98%

\[
\begin{array}{c}
\text{H}_2 \\
\text{H}_2 \\
\text{PPh}_3 \\
\text{PPh}_3 \\
\end{array}
\]

2%

\[
\begin{array}{c}
\text{P}_2\text{Rh} \quad \text{Cl} \\
\text{P}_2\text{Rh} \quad \text{Cl} \\
\text{PPh}_3 \\
\text{PPh}_3 \\
\end{array}
\]

**Association**

**Addition**

Typically 10 turnovers per minute

**Migration**

**Elimination**

\[
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array}
\]

**P**

**2**

**Rh**

**Cl**
Now take the case of a chelating diphosphine under conditions that are relevant to asymmetric catalysis; typical pre-catalyst shown.

\[
\text{Me', PPh}_2 \quad \text{Me', PPh}_2 \quad \text{bis-(C}_7\text{H}_8\text{-)}\text{Rh BF}_4
\]

\[
\text{H}_2, \text{MeOH}
\]

\[
\text{(S,S)-CHIRAPHOS}
\]
The $^{31}$P NMR of diphosphine dialkene complexes CHIRAPHOS is distinctive, and changes cleanly under H$_2$ (proton-decoupled).

No hydrides! What would happen with PPh$_3$ as ligand under these conditions?
Adding dehydroamino ester (B→C) gives a new spectrum showing strong binding of the alkene to Rh

Why are there not two enamide complexes one for Re- and one for Si-bound alkene? Why 8 lines??

Enamide complex; Rh-coupled AB quartet means *inequivalent* P environments
The 8-line $^{31}$P NMR species (C) observable in the absence of hydrogen, now with DIPAMP (Monsanto)

Here both diastereomers are detectable by $^{31}$P NMR!
The $^{31}\text{P}$ NMR species observable in the presence of hydrogen only at low temperature
Alkene dihydrides have been elusive in Rh asymmetric hydrogenation.

\[
\begin{align*}
\text{P}_2\text{Rh} & \quad \text{H} \quad \text{H} \quad + \\
\text{CO}_2\text{Me} & \quad \text{NH} \quad \text{O} \quad \text{Me}
\end{align*}
\]

\text{NEVER OBSERVED !!}
When intermediate C is prepared in the DIPAMP Rh case then two sets of 8-line signals can be seen.

In a different Rh enamide case two sets of 8-line signals are seen in a ratio of 92:8.
A transient alkylhydride is seen at $-50 \, ^\circ\text{C}$ from the minor enamide – stable at this temperature.

By making the enamide complex at low temperatures a mixture rich in the less-favoured form can be formed. This is captured selectively by $\text{H}_2$, still at low temperatures.

Which hand of product is formed from this intermediate?
Rhodium asymmetric hydrogenation has been a rich source of reactive intermediates; all cations here:

![Chemical diagram]

Transient product complex

Computational chemistry indicates a further intermediate between the minor enamide and the dihydride at *. Suggest what this might be.
Kinetic analysis of asymmetric hydrogenation is broadly in agreement with NMR observations

Major contributor Jack Halpern - Chicago

Difference from Wilkinson’s catalyst - several NMR characterisable intermediates in the true catalytic cycle

Combination of kinetics of H$_2$ addition (vary pressure, temperature, concentrations of substrate and catalyst).

Coupled with NMR, UV, fast reaction kinetics - stopped flow.

Aim is to build a complete picture of the catalytic cycle
Principles of stopped flow kinetics; useful e.g. for measuring the rate of substrate binding to catalyst.
The full consequences of the kinetic analysis are shown here. Strong binding, cf Micaelis–Menten treatment – watch out for saturation!

$$k_2 \text{ (min)} \approx 700 \times k_2 \text{ (maj)} - \text{minor enamide pathway dominates}$$

From steady state:

$$\frac{d[R\text{-product}]}{dt} = k_2(\text{maj})K_1(\text{maj})[H_2][\text{Rh}]_{\text{tot}}/(K_1(\text{maj}) + K_1(\text{min}))$$

$$\frac{d[S\text{-product}]}{dt} = k_2(\text{min})K_1(\text{min})[H_2][\text{Rh}]_{\text{tot}}/(K_1(\text{maj}) + K_1(\text{min}))$$
Here’s the complete set of experiments; NB all the reactive intermediates are characterised by NMR.

The transient alkylhydride is not “seen” in the kinetics - What’s the reason?
Related topic; asymmetric synthesis by alkene isomerisation.

Principle:

\[
\begin{align*}
\text{H-Migration on the front side of the allyl shown; how would you carry out the reaction by reversible M-H addition to the alkene?}
\end{align*}
\]
The synthesis of menthol has an alkene isomerisation as the key enantioselective step.

Condensation of 2 x isoprene and HNEt₂
Nickel - catalysed

Solvent = THF or acetone

Catalyst

Several steps
(begin with hydrolysis of enamine)

Enamine, >95% e.e.

Find conditions for the remaining steps in menthol synthesis?
Appendix: A more detailed exposition of the Michaelis–Menten methods for analysing catalytic kinetic data
The historical basis for analysis of catalytic kinetics lies in the analysis of enzymes by Michaelis and Menten; simplified case presented here.

Scheme 1: Reaction sequence of the simplest case of Michaelis-Menten Kinetics. (E = catalyst, S = substrate, ES = catalyst-substrate complex, P = product, $k_i$ = rate constants)
Enzymologists have developed simple treatments for plotting and analysing kinetic data.

**Michaelis-Menten**

\[
\nu = \frac{\nu_{\text{max}} [S]}{K_{\text{MM}} + [S]}
\]

\[
\frac{1}{\nu} = \frac{1}{\nu_{\text{max}}} + \frac{K_{\text{MM}}}{\nu_{\text{max}}} \frac{1}{[S]}
\]

*K_{MM}* is the Michaelis (Menten) constant.

\(\nu\) is the reaction rate (velocity).

**Lineweaver-Burk**

\[
\frac{1}{\nu} = \frac{1}{\nu_{\text{max}}} + \frac{K_{\text{MM}}}{\nu_{\text{max}}} \frac{1}{[S]}
\]

Derivation of these equations is based on the *steady-state approximation*.

**Hypotheses:**

1. The concentration of [E.S] changes much more slowly that that of either [S] or [P].
2. At a set concentration [S]₀ initial rate of product formation varies linearly with [E]₀.
4. At a set concentration [E]₀ and high [S]₀ a maximum rate \( ν_{\text{max}} \) is attained.

\[
\begin{align*}
\text{Rate} & \quad v_{\text{max}} \\
[S] & \quad E + S & \Leftrightarrow & \ E.S & \rightarrow & \ P + E
\end{align*}
\]
Michaelis–Menten converts the data into something manageable

**Steady State Approximation:**

Rate of product formation \( \nu = k_2[ES] \)
Rate of reactant loss \( \nu = k_1[E][S] - k_{-1}[ES] \)

\[
\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0
\]

Reorganising:

From this: \( [ES] = \frac{k_1[E][S]}{k_{-1} + k_2} \)

Define \( K_{MM} = \frac{k_{-1} + k_2}{k_1} = \frac{[E][S]}{[ES]} \) units of Molarity

If the catalyst is in excess then: \( [ES] = \frac{[E]_0}{1 + K_{MM}/[S]_0} \)

Substituting into our definition of the rate:

\[
\nu = \frac{k_2[E]_0}{1 + K_{MM}/[S]_0}
\]

This is the Michaelis-Menten equation
Lineweaver–Burk type plots are easier to use in practice

\[ \nu = \frac{k_2[E]_0}{1 + K_{MM}/[S]_0} = \frac{\nu_{max}}{1 + K_{MM}/[S]_0} \quad \text{Michaelis-Menten} \]

Rearrange this:

\[ \frac{1}{\nu} = \frac{1}{\nu_{max}} + \left( \frac{K_{MM}}{\nu_{max}} \right) \frac{1}{[S]_0} \quad \text{Lineweaver-Burk} \]
`More IgNobel Prizes

IGNobel prizes: MEDICINE: Gregg A. Miller of Oak Grove, Missouri, for inventing Neuticles -- artificial replacement testicles for dogs, which are available in three sizes, and three degrees of firmness;
PHYSICS Andre Geim of the University of Nijmegen (the Netherlands) and Sir Michael Berry of Bristol University (UK), for using magnets to levitate a frog. PS 2010 and Graphene!

IGNobel Prizes: BIOLOGY: Norma E. Bubier, Charles G.M. Paxton, Phil Bowers, and D. Charles Deeming of the United Kingdom, for their report "Courtship Behaviour of Ostriches Towards Humans Under Farming Conditions in Britain."
PHYSICS Jack Harvey, John Culvenor, Warren Payne, Steve Cowley, Michael Lawrance, David Stuart, and Robyn Williams of Australia, for their irresistible report "An Analysis of the Forces Required to Drag Sheep over Various Surfaces."