Reaction Progress Kinetic Analysis to Probe Catalytic Reactions

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Reaction Progress Kinetic Analysis (RPKA)

- Simple method of interpreting large datasets and complex reactions obtained from continuous monitoring of a reaction
- Determines rate laws and elucidates significant information to reaction mechanism
- Can give the same information that classical kinetic approaches give, with considerably less experiments required
- Representative of realistic reaction conditions

RPKA process formalised by Donna Blackmond in late 1990’s
How Does it Work?

Two key components are:

• Continuous, accurate method of experimental data collection *in situ* eg. GC, calorimetry, FTIR, NMR
• Simple computational means of data manipulation

Integral measurements
• Rely on relationship between measurable parameter and species concentration

Differential measurements
• Measure the reaction rate directly as the primary measured parameter
Dealing with Complex Systems – [“Excess”]

- Classical experiments get considerably more convoluted when the system is more complex.
- RPKA can help cut down on time and effort of assessing these reactions without resorting to holding one concentration constant.
- Introduce [“excess”]

\[
\]

- The difference between initial concentrations of [1] and [2].
- Does not change over course of reaction (constant volume).

Figure – Simple catalytic reaction
How Does [“Excess”] Work?

- Substitute equation relating [“excess”] to initial concentrations into rate expressions gives a new rate expression

\[
v = \frac{a [1] [2] [4]_{\text{total}}}{1 + b [1] + c [2]}
\]

\[
a = \frac{k_1}{k_{-1}}, \quad b = \frac{k_1}{k_{-1}}, \quad c = \frac{k_2}{k_{-1}}
\]

\[
v = a' \frac{[\text{“excess”}] [1] + [1]^2}{1 + b' [1]} [4]_{\text{total}}
\]

\[
d' = \frac{k_1 k_2}{k_{-1} + k_2 [\text{“excess”}]}, \quad b' = \frac{k_1 + k_2}{k_{-1} + k_2 [\text{“excess”}]}
\]

- For a given set of conditions, [1] is now the only variable, with [“excess”], [4]_{total}, k_1, k_2 and k_{-1} no all constant
- As long as [“excess”] remains constant, monitoring the concentration of one substrate allows reactions with two substrates to be assessed
Same [“Excess”] Experiments

- Carry out several experiments with the same [“excess”] but varying concentrations of the substrates 1 and 2
- This is equivalent to carrying out the same experiment at different starting points
- Useful for probing reactions for issues eg. product inhibition, catalytic deactivation
- Overlaying plots of reaction rate for varying concentrations of substrates elucidates information

SE experiment for Heck reaction with two different sets of concentrations of aryl halides and olefins

Repeat SE experiment with product addition:
Overlay – Product inhibition
No Overlay – Catalyst deactivation

SE experiment for epoxide ring opening with two different sets of concentrations of epoxide and H₂O

ANGEW. CHEM. INT. ED. 2005, 44, 4302 – 4320
Example – ‘Elucidating the mechanism of the asymmetric Aza-Michael Reaction’

- Used SE experiments to examine the behaviour of the reaction over the course of the reaction
  - There was no overlap between 1 and 2
    - Catalytic deactivation or product inhibition occurring in 1
  - Overlap between 1 and 3 tells us that the cause of abnormality is product inhibition. Implemented into catalytic cycle
Example – Amino acid catalysed imine hydrocyanation

- Kinetic experiments showed that the hydrocyanation reaction was first order in both HCN and the imine, yet considerably less the 1 in the catalyst.

- Same [“excess”] kinetics was able to show that the deviation from the expected first order kinetics was not due to catalyst deactivation or product inhibition.

- Resulting conclusion was however that an inactive catalyst dimer was forming at high [cat]_{tot}, may have shown if SE experiment was performed at higher [cat].
Different [“Excess”] Experiments

- Vary [“excess”] over different experiments to probe substrate concentration dependencies
- Gives similar information to that obtained in classical kinetic studies i.e. order in various reactant concentrations – However requires fewer experiments.

• No overlay in (a) tells us that reaction is not first order
• Overlay in (b) confirms 0.5 order in [1]
Esterification of an alcohol – Detailed use of RPKA to elucidate mechanism

First order in catalyst

First order in anhydride (and alcohol)

No catalyst deactivation

No product inhibition

Applying RPKA in Own Project

- Copper catalysed Ullmann-Goldberg reaction

\[ \text{Br} + \text{H}_2\text{N}\text{Cyclopentane} \xrightarrow{\text{Cul, Ligand}} \text{Base, Solvent, } \Delta \to \text{N-Benzylpiperidine} \]

- Notoriously awkward and irreproducible
- Same ["excess"] experiments to prove presence of catalytic deactivation – not previously reported
- May elucidate information regarding catalytically inactive resting states in catalytic cycle