Catalysis and kinetics – David Fox (Warwick)

Catalysis is 1) important, 2) complicated and 3) often un-optimized



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Thinking about catalytic cycles





Noyori-type transfer hydrogenation of ketones



Actually, it is a three-step process with HCO₂H



Time-dependent analysis of product formation



But we can model it as two steps



Concs are all related to RuH₂ and alcohol product

$$\frac{d[A]}{dt} = k^{1}[RuH_{2}][K]$$
$$\frac{d[RuH_{2}]}{dt} = k^{2}[Ru] - k^{1}[RuH_{2}][K]$$

 $[K] + [A] = [K]_0$ $[RuH_2] + [Ru] = [Ru]_0$

$$\frac{d[A]}{dt} = k^{1} [RuH_{2}] ([K]_{0}-[A])$$

$$\frac{d[RuH_{2}]}{dt} = k^{2} ([Ru]_{0}-[RuH_{2}]) - k^{1} [RuH_{2}] ([K]_{0}-[A])$$

Rate of reaction / concentration of 2 species can be calculated.

Data can be fitted to evaluate 2 variables.

The concentration and therefore rates of reaction of the active catalyst and ketone are related.

Fitting data to the two coupled ODEs with MATLAB





Small changes in catalyst – significant changes in kinetics



Org. Lett., 2007, 9, 4659-4662

Multi-step kinetics require proper analysis





 $k^{1} = 8 M^{-1}min^{-1}$ $k^{2} = 2 min^{-1}$



 $k^{1} = 8 \text{ M}^{-1} \text{min}^{-1}$ $k^{2} = 2 \text{ min}^{-1}$



 $k^1 = 6$ $k^1 = 8.0000$ $k^1 = 10$ $k^2 = 2.35$ $k^2 = 2.0000$ $k^2 = 1.83$ (0.0106)(0.0000)(0.007)

Data with (artificial) measurement error



 $k^{1} = 8.1 \pm 0.6 \text{ M}^{-1} \text{min}^{-1}$ $k^{2} = 2.02 \pm 0.08 \text{ min}^{-1}$



 $k^{1} = 8.1 \pm 0.6 \text{ M}^{-1} \text{min}^{-1}$ $k^{2} = 2.02 \pm 0.08 \text{ min}^{-1}$



 $k^1 = 6$ $k^1 = 8.1$ $k^1 = 10$ $k^2 = 2.39$ $k^2 = 2.02$ $k^2 = 1.85$ (0.016)(0.012)(0.013)

The overall rate does not change much along the trench.

How can this be?

What does the trench mean?

What does this effect the catalytic cycle?









As you move along bottom of trench the curve "flexes" through points.

Little difference on error for real data

What is the difference between straight and curvy lines?

Is it anything to do with the rate determining step / catalyst resting state?

A hydroamination (Scott) – what is the RDS?



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A hydroamination (Scott) – what is the RDS? - Step 1



If "k² step" is RDS then rate α [ketone]⁰ – straight line If "k¹ step" is RDS then rate α [ketone]¹ – curve



Change in line shape = change in RDS



Change in RDS balance as you "flex" the curve



As you move along bottom of trench the curve "flexes" through points.

Change in RDS balance

Change in RDS balance as you move along trench



 $k^1 = 6$ $k^1 = 8.0000$ $k^1 = 10$ $k^2 = 2.35$ $k^2 = 2.0000$ $k^2 = 1.83$ (0.0106)(0.0000)(0.007)



Is there a way of increasing precision?

Can we get rid of the trench?

Can we learn any more about RDS?

Have we measure and use more information?



We have measured the concentration of this only.

Product concentrations only



Catalyst concentrations only



Catalyst concentrations only


RMS error for array of k¹ and k² (product only)



 $k^{1} = 8 \text{ M}^{-1} \text{min}^{-1}$ $k^{2} = 2 \text{ min}^{-1}$

RMS error for array of k¹ and k² (catalyst only)



 $k^{1} = 8 \text{ M}^{-1} \text{min}^{-1}$ $k^{2} = 2 \text{ min}^{-1}$

Product and catalyst concentrations



Combined RMS error (line v data) for array of k¹ and k²



 $k^{1} = 8 \text{ M}^{-1} \text{min}^{-1}$ $k^{2} = 2 \text{ min}^{-1}$

Is this just a problem for transfer hydrogenations?

Catalytic conjugate addition / lactonization (Smith)



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Catalytic conjugate addition / lactonization (Smith)



Essentially a three component – two step process



Both reactions are (probably) second order enolate formation: rate α [cat][anhydride] Lactone formation: rate α [cat][enone]

Log plots show order (or not) of reaction components



Log plots show order (or not) of reaction components





- 1) Catalyst acylation is fast and reversible.
- 2) RDS is enolate formation.

 $k_{\rm H} / k_{\rm D} = 3.8$

3) Conjugate addition / cyclisation is fast

And, if you believe these things, so does DFT



A general case of two second order reactions



Both reactions are second order k^1 step: rate α [catA][reactant] k^2 step : rate α [catB][reagent]

A general case of two second order reactions





RMS error (line v data) for array of k¹ and k²



The trench is WORSE! $k^1 = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^2 = 10 \text{ M}^{-1}\text{min}^{-1}$

There are infinite solutions where error is zero!



 $k^{1} = 15 \text{ M}^{-1}\text{min}^{-1}$ $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{1} = 7.5 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 7.5 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 15 \text{ M}^{-1}\text{min}^{-1}$



 $k^{1} = 15 \text{ M}^{-1}\text{min}^{-1}$ $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{1} = 7.5 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 7.5 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 15 \text{ M}^{-1}\text{min}^{-1}$



RMS error (line v data) for array of k¹ and k²



The trench is orthogonal! $k^1 = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^2 = 10 \text{ M}^{-1}\text{min}^{-1}$

There are infinite solutions where error is zero!



RMS error (line v data) for array of k¹ and k²



 $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$

There is only one solution where error is zero!

A general case of two second order reactions



Both reactions are second order k^1 step: rate α [catA][reactant] k^2 step : rate α [catB][reagent]

Analysis of product formation with 2 eq. reagent



RMS error for array (2 eq reagent) product only



 $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$

Analysis of product formation with 2 eq. reagent



RMS error for array (2 eq reagent) catalyst only



 $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$

RMS error for array (2 eq reagent) prod. and cat.



 $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$

Analysis of product formation with 0.5 eq. reagent



RMS error for array (0.5 eq reagent) product only



 $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$

Analysis of product formation with 0.5 eq. reagent



 $k^2 = 10 \text{ M}^{-1} \text{min}^{-1}$

RMS error for array (0.5 eq reagent) catalyst only



 $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$

RMS error for array (0.5 eq reagent) prod. and cat.



 $k^{1} = 10 \text{ M}^{-1}\text{min}^{-1}$ $k^{2} = 10 \text{ M}^{-1}\text{min}^{-1}$

A problem? A solution?

If you can measure the relative concentrations (resting state ratio) of the catalytic species then you can remove parameter interdependence.

And at the same time learn far more about RDS?

Acknowledgements

Chemistry:

Prof. Martin Wills (Warwick) Prof. Peter Scott (Warwick) Prof, Andrew Smith (St. Andrews) and their group members

Analysis: Dr Paul Griffiths (Cambridge) Dr John Earl Prof. George Rowlands (Warwick)

Asymmetric Transfer Hydrogenation of α-chloroketones 1



Asymmetric Transfer Hydrogenation of α-chloroketones 2




Asymmetric Transfer Hydrogenation of α-trichloroketones



Asymmetric Transfer Hydrogenation of α-chloroketones - heterocycles





