"Introduction"

- Not much needed -- case studies.

- While there aren't a tremendous amount of these "problem-solving through kinetics" stories out there, the ones that are out there are typically beautiful pieces of work. They elegantly solve problems logically, that may well have taken a very long time if attempted though the more discovery-minded trial-and-error. These types of problems, however, would not typically be important to a discovery synthesis, and so the same rigorous undertaking is not necessary. As you'll see, process chemists have to think differently, and kinetics is one avenue they can take to problem-solve.

- The studies were chosen because they do just that, solve synthesis/scale-up problems through use of kinetics. There are other studies out there that just probe the kinetics of reactions for the sake of (for lack of a better word) science. This talk was limited to the "problem solving" aspect.

- This talk was also limited to Organic Processes and Research Development. While I'm sure there are other sources out there for this type of information, OPRD is certainly the best.

- "Texty" slides are a necessary evil--my apologies.


- A great study that will not be discussed (for reasons of time constraints) involves the mechanism of the Noyori transfer hydrogenation of imines. The mechanistic system is more complex than that of the ketone/alcohol system as a result of "complications" arising from the higher basicity of imine/amine system: Org. Proc. Res. Dev. 2006, 10, 457.
Pilot plant development of an \( \alpha_v \beta_3 \) integrin antagonist. This integrin is essential for angiogenesis and is therefore a good cancer target. Pfizer.

Retrosynthetic Strategy:

1st generation: Asymmetric Michael addition

![Diagram of 1st generation retrosynthetic strategy](image)

Excellent approach. Notably, Michael addition occurred at higher temperature than anticipated, and the combination of MOM group with tert-butyl ester provided excellent diastereoselectivity (>98%). Abandoned because later hydrogenation reduced aryl bromide.

2nd generation: Asymmetric enamine reduction

![Diagram of 2nd generation retrosynthetic strategy](image)

While enamine could be procured in 70% overall yield, the maximum of 70% ee in the hydrogenation led to the abandonment of this method.

3rd generation: Resolution of racemic product

![Diagram of 3rd generation retrosynthetic strategy](image)

This approach offered synthetic feasibility on scale, but the resolution proved problematic. On laboratory scale resolution was best with (-)-CSA it give 91% ee. Scale-up, though, elicited decreased ee (53%), due (at least in part) to the second problem: the chiral salts were gelatinous salts making them very difficult to work with.

4th generation: Diastereoselective Reformatsky reaction

![Diagram of 4th generation retrosynthetic strategy](image)

Best approach yet. Excellent overall ee. In spite of many potential scale problems, this route was chosen for development because the major chemical problems were addressed (high yield and \( \text{dr} \)). Problems: MEMCl toxicity; isolation of unstable imine; Reformatsky reaction highly energetic; \( \text{Pb(OAc)}_4 \) say no more; inconsistency in purification of final product.

"Furthermore, the enabling technology involved twelve phase separations, six distillations, three isolations, two \( \text{MgSO}_4 \) dehydrations, one crystallization, and two drying steps. These features tied closely with issues such as safety, engineering, cost of goods, resource allocation, raw materials sourcing as well as the business strategy were the emphasis behind further development of the imino-Reformatsky route to [the product]."
Removal of MEMCI from synthesis. Unfortunately, other PG's tried resulted in either lower d's, or incompatibility with downstream chemistry. Unfortunately, the MEM group was deemed a necessity. Because of this, safety protocols were developed for the on-scale use of MEMCI, as well as the destruction of the excess reagent post reaction.

Determining the 2nd order rate constant for the hydrolysis of MEMCI. Used ReactFTIR, recording spectra every 1.4 seconds for 10 min.

The reaction was repeated in an NMR tube and, through use of precise timing this rate constant was corroborated.

The experimentally determined rate constant implies that the all of the excess MEMCI should be quenched if the reaction was allowed to stir with water at room temperature for one hour.

Quantitative GC experiments were then conducted. A control reaction of MEMCI in anhydrous DMF showed that the reagent persisted even after 83 minutes. However, a 1/1 DMF/H₂O mixture resulted in complete destruction of the reagent after 21 minutes.

Additionally, analysis of the MEM protected phenol isolated after stirring with water for 1 hour had no detectable MEMCI, whereas if the reaction was only stirred for ten minutes, there was reagent in the samples.

Another point of interest was observed in the conducting of the reaction. Mode of quench was important. That is to say, if water was added to the reaction mixture, the product crashed out laced with MEMCI that could not be destroyed even if stirred for an hour. In the practiced pilot procedure, the reaction was transferred (1) to a DMF/water mixture and stirred for 30-60 minutes before the product was collected by filtration/centrifugation.

Instability of imine: The imine formation on the first pilot operation led to complete decomposition. After arduous testing, it was discovered that the phenylglycinol used in the pilot process was from a different manufacturer, and for reasons never fully elucidated, led to a 2000% longer rate of imine formation.

The decomposition turned out to be a separate problem. The process involved imine formation in THF, evaporation of the solvent to dryness (to remove water), then recharging with NMP for the Reformatsky reaction. The evaporation to dryness was found to be the source of the decomposition. Use of NMP for this process lead to slower imine formation (20 hr, slow, but acceptable), and after filtering through a column of untreated molecular sieves, the imine was in solution and ready for the Reformatsky reaction. This method of dehydration proved very robust for the process, important as water was shown to be detrimental to the Reformatsky reaction.
The chemists used thermokinetic data (essentially predicting exotherms) in order to more safely design scaled-up reactions. Perhaps not surprisingly, generation of the Reformatsky reagent required the most care, particularly because experiments showed a 15-minute induction period where there was essentially no heat released. The hard data as well as a summary thereof is below, although a detailed discussion of it will be left to the reader. Needlesstosay, this data was extremely helpful in safely designing the experiment.

Changing from lead tetraacetate to sodium periodate seemed like a trivial enough change and, a priori, it was. The waste disposal issues associated with lead had seemed to have been solved. A large amount of side product (below) was, however, observed. The product was formed as a mixture along with 23% of the undesired oxazolidine.

This was solved by the addition of methylamine to the reaction as a scavenger for the formaldehyde formed in the reaction mixture.

Ethyl ester formation was operationally extremely cumbersome: 4 solvents, two distillations, and a crystallization (with some decomposition). While intensive optimization was not able to idealize this process, enough was learned to streamline the process somewhat, and avoid the decomposition problems.

Using all of the above modifications, the pilot plant campaigns procured 591 kilograms of the β-amino-ethylester tosic acid salt.
Identification of new catalysts to promote imidazole couplings and optimization of reaction conditions using kinetic modeling. Pfizer.

\[ \text{N,N'-carbonyldiimidazole is commonly used as an acid activator for coupling reactions. There are advantages to using CDI: price -- $8/\text{mol} \ (\text{large-scale purchase}), \text{and the byproducts are the innocuous CO}_2 \text{ and imidazole. It is not without its problems though. The acyl imidazole is less reactive than, for instance, the corresponding acid chloride. As a result, particularly hindered acids or weakly nucleophilic amines often result in poor yields, or unacceptably long reaction times when done on-scale. In order to circumvent this problem, a catalyst is often used that can activate the carbonyl even more than the acyl imidazole. HOBt is one such catalyst. The potential for process use of HOBt is limited by several factors, though. When heated beyond its melting point, it is known to explode (156°C). As a result, transporting large quantities of the substance in Europe is subject to restrictions.} \]

Screening potential catalysts (for catalytic activity) led to two additional hits:

- \[ \text{N-hydroxybenzotriazole (HOBt)} \]
- \[ \text{2-hydroxypyridine (HOPy)} \]
- \[ \text{endo-N-hydroxy-5-norbornene-2,3-dicarboximide (HONB)} \]

While the exact structures of the reacting partners were not disclosed in this paper, the general reaction that was studied was as follows:

\[ \begin{align*}
\text{R} & \text{O} \quad \downarrow \quad \text{H}_2\text{N}\cdot\text{Ar} \quad \text{cat.} \\
\text{N} & \quad \text{H} \quad \text{N} \quad \text{Ar} \\
\end{align*} \]

**Figure 2.** Differential scanning calorimetry results of HOBt, HOPy, and HONB.

This shows that HOPy is completely thermally stable, and HONB is moreso than HOBt. Also, HOPy is also the cheapest of the three, and HONB is the most expensive.

As a starting point for the investigation, the catalytic efficiency of HOBt was analyzed and three different loading levels:

\[ \begin{align*}
\text{0.88eq} & \quad \nwarrow \quad \text{0.44eq} & \quad \nwarrow \quad \text{0.22eq} \\
\end{align*} \]

**Figure 3.** Solution yield (\%) of amide 6 with different levels of catalyst, HOBt, in boiling EtOAc.
Even though HOPy and HONB seem to be better candidates in terms of thermal stability they still need to provide acceptable yields and reaction rates for process use. This was determined at two different catalyst-loading levels for the three catalysts (44 and 88 mol%). From this study, it is clear that the order if catalytic efficiency is HOBt > HOPy > HONB.

When comparing HOPy and HONB, HOPy is superior in terms of catalytic efficiency, cost, and thermal stability. HONB was no longer considered.

"In chemical development, reaction time is not always the rate limiting factor in a process; in fact, workup, filtration, and drying are often the rate-limiting operations."

For this project, it was determined that the goals were 24 hr reaction time and a reaction completeness of 95%. It was clear that HONB was not going to meet these requirements. It was also clear that HOPy would not reach these specifications at stoichiometric amounts in refluxing ethyl acetate. To guide further experiments, a kinetic model was pursued.

"To the chemist or engineer on academic or discovery chemistry, optimization of a reaction often means devising conditions that simply lead to the best yield. To the industrial chemist and engineer involved in research and development, optimization may refer to a combination of factors such as yield, cost, efficiency, or throughput, and several of these experimental responses may have to be optimized concurrently."

The researchers used Dynochem software to do the kinetic modeling for their experimentally determined data. This would for predictability of other reaction conditions. For HOBt (in boiling ethyl acetate), the rate law was assumed to be 3rd order and the concentration of catalyst was assumed to be constant (as the catalyst is regenerated in the reaction).

\[
\text{rate} = k[5][4][\text{HOBt}], \text{ where } k = 3.70 \times 10^{-4}\text{mol}^{-2}\text{s}^{-1}
\]

The same was done for HOPy in boiling ethyl acetate and, not surprisingly, a smaller rate constant was found.

\[
\text{rate} = k[5][4][\text{HOPy}], \text{ where } k = 2.43 \times 10^{-4}\text{mol}^{-2}\text{s}^{-1}
\]

In order to extrapolate these data for different temperatures for HOPy, a modified Arrhenius equation was used to obtain the activation energy (49.9 kJ/mol), thus allowing the calculation of rate constant as a function of temperature.

The assumption was made that the kinetics for n-propyl acetate would behave similarly to that for ethyl acetate at the same concentration and temperature. So, optimum cat. loadings are predicted as follows: HOBt/EtOAc: 0.12 equiv. HOPy/EtOAc: 1.76 equiv. HOPy/n-PrOAc: 0.44 equiv

These were verified by actual experiments (Figure 6). "Of course if, for some reason, the target conversion and/or target reaction time changed, i.e. there is a need to increase throughput and reduce reaction time, the new optimized conditions can be simulated from the current models and accurately predicted."
Understanding of the origin of unusual stepwise hydrogenation kinetics in the synthesis of the 3-(4-fluorophenyl)morpholine moiety of NK1 receptor antagonist Aprentant. This is the active ingredient in Emend, currently marketed for chemotherapy-induced nausea/vomiting. Merck.

Upon acid charge, a complex equilibrium of five chemical entities exists. At low pH (< 1.0 equiv. acid relative to Grignard), hemiaminals dominate with small amounts of methyl aminals and amine below. At higher pH, the ring-opened ketone dominates (high basicity of secondary amine).

These ratios, and therefore the equiv. of acid added, had a profound influence on the rate and selectivity of the hydrogenation. When < 1.0 equiv. acid is employed, very little product is formed and the reaction is mostly the mixture. As amount of acid increases, so does product (95% at 1.3-1.4 equiv.) before dramatically dropping to 50% at 1.66 equiv (remaining material is imine below) and zero at > 1.7 equiv. (remaining material is unreacted ring-opened ketone).
Rate of formation of 19 and 20 reaches a maximum at the same conditions as maximum product formation (1.3-1.4 equiv.).

Mechanistic conclusions:
- At basic conditions, aminals will dominate, and formation of 18 will be slow, impeding 19/20 formation and hydrogenation of 14. Direct debenzylolation of 9-12 is also likely slow (reference to this effect). With all other reactions slow, the ketone reduction 13 can compete (in spite of 13 being present in just minor amounts), and indeed 15/16 are observed.
- At slightly acidic conditions (1.0-1.6 equiv.), a preequilibrium between 9-12 and 18 is relatively fast. But now, debenzylolation of 9-13 to give 17 is much faster than the rearrangement to 19/20, or ketone reduction to 15. If very acidic conditions (> 1.6 equiv.), 13 dominates the original Grignard adduct composition. Apparently, ketone reduction and debenzylolation of 13 are slow, and no rearrangement to 19/20 can occur b/c equilibrium lies completely to the side of 13.

All mechanism elucidation work was discovery scale. The efficiency after crystallization as the HCl salt was 89-94% overall yield, 350:1 dr, and 99.7 area % purity (HPLC). This corresponds to each step (one nucleophilic addition and two reductions) occurring at > 95% efficiency.

When first performed on multi-kilo scale, up to 0.5 area % defluoro was observed. The Grignard was checked and was devoid of phenyl Grignard. Defluorinated product (8) increased with the aging of the hydrogenation mixture at a rate of < 0.01 area % per hr. This needed to be worked out, and a goal was set for < 0.1 area % total.

It was thought that hydrogen mass transfer effects could be responsible for variable kinetics observed in the hydrogenation step. For intrinsically fast hydrogenations, hydrogen transport b/w the gas/liquid interface can be rate-limiting. Gas/liquid mass transfer is first order with the overall rate being governed by $k_l a$ and the difference between the actual and saturated solution concentrations of $H_2$ (which is a function of headspace pressure): rate = $k_l a([H_2]_{sat} - [H_2])$. Obviously, a major factor governing $H_2$ uptake is agitation rate, so this was probed at 500 and 1000 rpm.

The reaction appears to be operating at hydrogen diffusion limitations. At 500 rpm, it is apparently zero order in substrate, b/c the rds is hydrogen mass transfer, and pseudo 1st order in $[H_2]$ (due to constant headspace pressure). Most importantly, the amounts of 8 isolated for 500 and 1000 rpm were 0.23 and 0.02 area % respectively.

**Figure 3.** Comparison of the rate of hydrogen uptake for hydrogenations using agitation rates of 500 and 1000 rpm ($k_l a = 0.03$ and $0.3$ s⁻¹, respectively). The substrate solution was
Monitoring the reaction by LCMS showed the above. Just trace amounts of 14 were observed during the course of the reaction, indicating that this is probably not a viable intermediate in the mechanism to product. Rather, imine 17 is observed at 90% assay yield at the midpoint of the reaction. The linear slopes for 7 (product), 17, and PhMe indicate the zero order nature of the reaction imposed by the hydrogen mass transfer limitation. Perhaps most surprising from Figure 4 is that these reactions occur in nearly perfect stepwise fashion. Final mechanism: Grignard adducts 9-13 are debenzyolated, to give imine 17. Importantly, almost no imine 17 is reduced to 7 before the starting Grignard adduct mixture is debenzyolated.

Why is this odd kinetic behavior observed? To determine, must use conditions where max rate of H2 intake is ~10x faster than that of the max intrinsic reaction rate: 2000 rpm reaction rate, 20 psig H2 pressure, and 2 wt% catalyst.

The rate of debenzylation shows a broad peak toward the beginning of the reaction, before slowly tapering off. Imine reduction, though, gradually increases until the spike (135 min) followed by rapid decrease. The point b/w the maxima explains the apparent zero order in hydrogen intake as the rates cancel each other out.

How does all of this explain the kinetics? If the Grignard adducts are strongly bound to the catalyst, but slowly hydrogenated, and the imine is weakly bound to the catalyst, but quickly hydrogenated, this would explain the reaction in the H2 intake is rate limiting scenario, but not in the saturation experiment, as ~30% of the imine is reduced before the rate spike. Clearly, H2 binding must be considered. If one assumes simultaneous binding of Grignard adducts, imine, and H2, this combined with the earlier assumptions explain the spike, but doesn’t adequately explain the quasi-zero order kinetics of the debenzylation, nor does it explain the kinetics of the mass transfer limited conditions. The final explanation offered is as follows: Grignard adduct actually reacts more quickly with surface-bound H2 than does imine, effectively inhibiting the reduction of the later by scavenging all of the available activated H2. Assuming this leads to a complicated NON-STEADY STATE scenario, nicely discussed in the paper, but an “author-admitted” fragile hypothesis. Bottom line: formation of 8 is favored at low H2 pressure cond’s. Why? This reaction is slow. As a result, the rate of defluorination is not affected by hydrogen pressure, whereas the imine reduction is slowed to the rate of the H2 mass transfer limitation. The net effect is a longer residence time of 17 in the reactor and a higher level of 8. The following actions were taken.

1. Catalyst loading reduced from 10-15 to 3-6 wt %.
2. [H2] increased by increasing pressure from 5 to 20 psig.
3. The g/l mass transfer rate was increased by maximizing the agitation rate.

Each of these factors was independently shown to diminish the levels of 8 formed in the reaction. In combination, formation of 8 was reduced to a nondetectable level.

Figure 4. Reaction profile of the hydrogenation performed at relatively low agitation (kL,a = 0.03 s⁻¹). The hydrogenation was
Figure 5. Hydrogen uptake rate profile for a typical hydrogenation reaction conducted under non-mass-transfer-limited conditions. Substrate solution (425 mL) prepared as described
Figure 6. Profile determined by LC-MS analysis of reaction samples for a typical hydrogenation conducted under non-mass-transfer-limited conditions. Substrate solution (425 mL) pre-

Figure 7. Instantaneous rate profiles of debenzylation and imine reduction calculated from the first derivatives of LC-MS concentration profiles shown in Figure 6.

Figure 8. Figure 9.
Synthesis of the CETP inhibitor torcetrapib: the resolution route and origin of stereoselectivity in the iminium ion cyclization. Pfizer.

Torcetrapib is a molecule that is being developed as a atherosclerosis and coronary heart disease.

The aza Diels-Alder approach was known to give the desired cis geometry around the tetrahydroquinoline ring system and therefore seemed like a good starting point.

Initial conditions led to product, 6, but in low yield (40-60%) in only 70% purity. After multiple optimization experiments failed, it was decided that imine 3 was not being formed cleanly. Analysis of the reaction mixture showed significant amounts of 4, which was thought to be the source of the problem. Thus, a two step procedure was devised where the imine was first intentionally trapped with a nucleophile, and subsequently unveiled for the Diels-Alder reaction in situ. Benzotriazole was employed. This not only was effective, but also avoided the use of TiCl₄ and BF₃·Et₂O.

Under these conditions, the process was thought to be stepwise.

Completion of the synthesis.

In none of the synthetic studies was any of the trans isomer detected. The authors found this stereoselectivity curious and decided to investigate the mechanism a little further using molecular modeling.

"Stereoselectivity, as a general phenomenon, arises from free energy differences associated with diastereomeric transition states (kinetics) or products (thermodynamics)."

In this stepwise mechanism, there are four possible cyclization product diastereomers. Of these four, only the two depicted were found to reside in energy minima.
The calculated energy difference between 16 and 18, and 17 and 19 were –0.8 and –0.3 kcal/mol respectively. This does not explain the observed stereoselectivity, and so a kinetic consideration had to be investigated.

In the stepwise mechanism, 15 is presumed to be the precursor to the cyclization. Accordingly, the two conformations shown below were found to be of lowest energy (along w/a 3rd non-productive conformer), and the transition states geometries were minimized as well. RC1 represents a global minimum in conformational space (MP2 level) and is 3.0 kcal/mol lower in energy than that for RC3. The energy difference is 4.4 kcal/mol for the corresponding transition state structures.

When this transition state energy difference of 4.4 kcal/mol is considered mathematically and plugged into the Arrenhius equation, 
\[ \text{cis/trans} = e^{(\Delta G_{\text{TS cis}} - \Delta G_{\text{TS trans}})/R \cdot T} \]
the predicted reaction stereoselectivity (cis-to-trans product ratio) is 99.9%.

"Therefore, the origin of the stereoselectivity takes place from a noticeably more stable reactant conformer and the lower activation energy for the cis cyclization."
A surprisingly low energy of activation is calculated for the system, though, particularly for the cis. This is due to the underestimated stabilization of the cation 15 by the counterion that is implicit in the solvation model (DMSO). This stabilizes the transition state less than the ground state conformations, because the charge is more diffuse, and thus inherently stabilized, in the bond-forming process. A sort of opposite stabilization effect is seen for the interconversion barrier between the two reaction conformers. The authors suggest TS31 should be more stabilized by this counterion effect than either conformation because of its "higher polarity."

![Diagram showing energy changes between cis and trans forms](image)