Communicating Research to the General Public

At the March 5, 2010 UW-Madison Chemistry Department Colloquium, Prof. Bassam Z. Shakhashiri, the director of the Wisconsin Initiative for Science Literacy (WISL), encouraged all UW-Madison chemistry Ph.D. candidates to include a chapter in their Ph.D. thesis communicating their research to non-specialists. The goal is to explain the candidate's scholarly research and its significance to a wider audience that includes family members, friends, civic groups, newspaper reporters, program officers at appropriate funding agencies, state legislators, and members of the U.S. Congress.

Over 20 Ph.D. degree recipients have successfully completed their theses and included such a chapter.

WISL encourages the inclusion of such chapters in all Ph.D. theses everywhere through the cooperation of Ph.D. candidates and their mentors. WISL is now offering additional awards of $250 for UW-Madison chemistry Ph.D. candidates.

Wisconsin Initiative for Science Literacy

The dual mission of the Wisconsin Initiative for Science Literacy is to promote literacy in science, mathematics and technology among the general public and to attract future generations to careers in research, teaching and public service.

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May 2014

Interception and characterization of catalyst species in rhodium-bis(diazaphospholane)-catalyzed asymmetric hydroformylation

by

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A dissertation submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

(Chemistry)

at the

UNIVERSITY OF WISCONSIN – MADISON

2014

My research explained for a broader audience

Looking closely at chemical reactions

Why look at chemical reactions?

Chemical reactions are going on all around us, all the time. We're surrounded by (and full of) molecules tumbling around each other and joining together to make new molecules, molecules coming apart into their constituent parts. Some of these reactions, you might pay attention to: drain cleaner foaming up into the sink as the strong bases in it react with water, or sugar caramelizing in a pan of browning onions. But most of them go on invisible, unnoticed.

Except by chemists.

The mystery of turning on thing into another can be as irresistible as alchemy, even if you're not making gold (and let's face it – you're not). Fascinating as they are, though, we also need chemical reactions to be useful: we rely on them to make most of the things we encounter every day. Most of the time, there's more than one way to combine the atoms and molecules in a reaction. Even in a simple made-up case like this one:

Figure 6.1. A simplified representation of what happens in a chemical reaction. Two things combine – and there's usually more than one way to do it.

Now, maybe those two possible products are both okay. But maybe not: maybe they act differently in some context, and you only want one of them. Any time you start letting atoms interact, you run the risk of getting products you don't want. How can you understand how to tweak the reaction until you only get the product you want? One of the best ways is to look at how the molecules interact.

Why hydroformylation?

My research focused on a reaction called hydroformylation. It's a useful reaction because it takes a molecule that's relatively simple – in some cases, only carbon and hydrogen – and makes it more interesting (and, not incidentally, more valuable) by tacking on an oxygen atom in addition to another carbon and hydrogen (usually with a metal-containing compound thrown in to make the process faster – more on that later). These "value-added" molecules produced by hydroformylation are aldehydes.

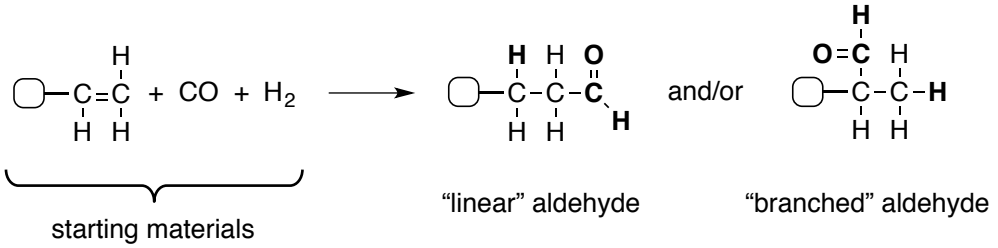
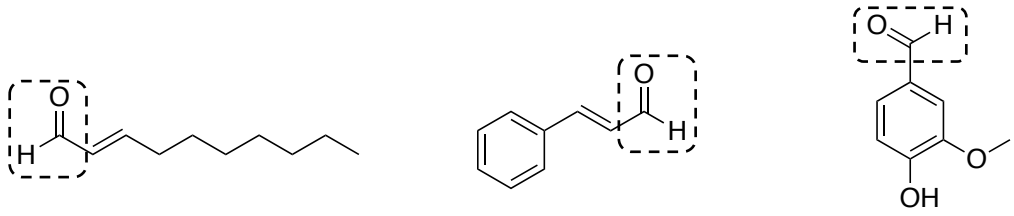


Figure 6.2. Hydroformylation makes aldehydes, molecules with a carbon/hydrogen/oxygen group attached to one of the carbon atoms of the starting material.

You're most familiar with aldehydes – even though you may not know it – as the molecules that produce a lot of common scents. That love-it-or-hate-it soapiness of cilantro? Aldehydes. The aromatic spiciness of cinnamon and vanilla? Aldehydes.



***E*-2-decenal**
cilantro

cinnamaldehyde
cinnamon

vanillin
vanilla

Figure 6.3. Aldehydes you're probably encountered in your kitchen. The C/H/O grouping – in the boxes – is what makes each of these molecules aldehydes.

Most of the aldehydes produced by hydroformylation – about eighteen billion pounds of them – are less exotic. For the most part, they're bulk chemicals, used to make things like detergents that get churned out on huge scales. Practical, but not very interesting.

Selectivity makes all the difference here. During hydroformylation, the carbon/hydrogen/oxygen trio (the aldehyde group) is added to one carbon of the starting material; the other carbon just gets a new hydrogen. Adding the aldehyde to the carbon at the end of the molecule – called the "linear" product because all the carbon atoms in the new molecule are in a single-file line – makes those bulk chemicals.

But the other product, where the new carbon and oxygen are attached to the inner position, is special. This addition makes a branch off the central spine of carbon atoms, and that branch puts these aldehydes in a class of molecules called "chiral." Molecules

exist in three dimensions (an easy point to forget, since we're always drawing them in two dimensions), and molecules like these branched aldehydes have four different arms sticking out in different directions.

The key point is that each of these arms is different, like an indecisive four-legged starfish. Each molecule like this has an almost-twin: another molecule, with the same four arms as this one, just in a different three-dimensional arrangement, the first molecule's mirror image. These pairs of fraternal twins are called enantiomers.

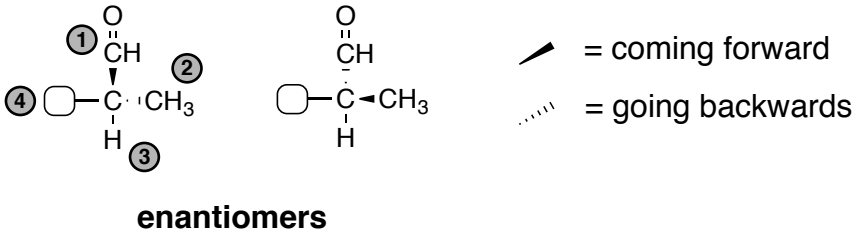


Figure 6.4. The branched aldehydes produced by hydroformylation are chiral: they have four different "arms" that, in three dimensions, can be arranged in one of two ways. In the aldehyde on the left; the aldehyde (CHO) group is pointing out of the page towards you, and the CH_3 group is pointing backwards, away from you. In the aldehyde on the right, their directions are switched. These *enantiomers* look almost the same, but they can react in very different ways.

Enantiomers might look the same, but they don't always *act* the same. Your right and left hands – the most familiar physical enantiomers – look similar, both can open doors and hold spoons and (sort of) write. Good luck, though, getting your right glove to fit on your left hand.

Most reactions that produce chiral molecules make both enantiomers, and they're not always separated. That can have serious consequences in pharmaceutical chemistry, for example, because many drugs are chiral. The best-known, and most tragic, case was what happened with thalidomide in the late 1950's. The thalidomide given to pregnant women to treat morning sickness wasn't separated into "right-handed" and "left-handed" molecules, and while one enantiomer did ease nausea, the other caused devastating birth defects. Even if one half of a chiral pair isn't actually harmful, some simply work better than others. The popular antidepressant Lexapro is a single enantiomer; its predecessor, Celexa, contained a mixture of the active and inactive enantiomers.

Aldehydes are really useful chemical precursors, because they can easily be turned into other things. The chiral branched aldehydes could be great candidates for use in making pharmaceuticals and other "fine chemicals" – specialized, lucrative molecules that are typically made on a small scale. Because enantiomers function so differently, especially in a biological context, if we want to use hydroformylation to make these valuable chiral molecules, we need it to be selective. We'd also like it to be fast.

That's where that metal compound comes in.

What's rhodium doing in there?

Catalysts make reactions faster by reducing the amount of energy it takes to turn the starting materials into the products. Metals, it turns out, have a special aptitude for this, and rhodium is a particular favorite. A lot of the world's rhodium is busy cleaning exhaust in cars' catalytic converters; some if it finds more aristocratic work in in the jewelry industry, where it's used to give a shiny, protective coating to platinum and white gold. In chemistry labs, though, it's used as a catalyst for a wide range of chemical

reactions. In our case, stuck to two phosphorus atoms, with some carbon, hydrogen, oxygen, and nitrogen atoms for decoration, rhodium works hard at hydroformylation. This particular catalyst makes just one enantiomer of the branched aldehyde most of the time (about four times out of five, on average) and is really fast: it can make more than one aldehyde per second.

What does it mean, though, to reduce the amount of energy a reaction takes?

Imagine you're making a cake. (Food metaphors are ubiquitous in chemistry – both fields involve mixing things together to make other, more desirable, things, and there's so much obvious chemistry in cooking that there's whole subcategory of cookbooks explaining how to use an understanding of chemistry to improve your results in the kitchen.) You're going to have to mix all the ingredients together somehow. You could do it by hand. That requires a lot of energy, though, and in this age of electronic conveniences you're out of practice, so it would probably take you a while.

So you'll probably use an electric mixer. Like a catalyst, it keeps you from having to use as much energy, so the process goes faster – and if you're making cakes on a grand scale, you can bake more than you could if you had to mix every one by hand (obviously a bonus). Other important points about catalysts: the starting and ending points of the process don't change (you start with ingredients and end up with cake batter whether you mixed it with a spoon or an electric mixer) and the catalyst itself isn't used up (once the batter is mixed, the mixer is available for the next round).

In chemical reactions, catalysts can also have a major effect on selectivity. The catalyst interacts with the substrate molecules to join them together. The specifics of that interaction can determine which product you get out. Is it easier to have molecule A

upside down or right side up? Does the catalyst prefer to the first carbon atom of A, or the second one? Is it easier to bind B first, and then A, or A first, and then B? Just like mixing the flour and sugar together before you add the butter could be a baking disaster, the particular way a chemical catalyst interacts with the starting materials can make all the difference in whether you get the product you want – or just a mess.

If we knew exactly how the catalyst was interacting with those molecules, we might be able to figure out why the reaction goes the way it does – and how to make it more selective.

But of course, these molecules are way too tiny for us really look at them directly, the way you might study workers on an assembly line to see how a car gets made. So we have to be creative. Chemists have spent decades devising techniques to squeeze information out of molecules we can't see. Most of these involve bombarding molecules with some type of radiation – visible light, ultraviolet light, x-rays – and seeing what bounces back. One of the most useful of these, called "nuclear magnetic resonance" (NMR), uses radio waves and giant magnets to tell us what molecules look like.

Looking at something too tiny to see

In the early nineteen-forties, the wartime demand for radar technology had physicists spending a lot of time thinking about radio waves. One of the products of these studies was the realization, by two separate scientists, that the nuclei of certain atoms could absorb radio-frequency energy when held in a magnetic field.

An odd number of protons, or neutrons, or both, gives an atomic nucleus a special ability to act like a tiny magnet. Put these miniscule magnets inside the magnetic field of a much bigger one, and they'll line up with it like iron filings arranging themselves in

lines around a magnet. But if you hit these nuclei with *just* the right amount of radio-frequency energy, they can be persuaded to flip, and line up the opposite way.

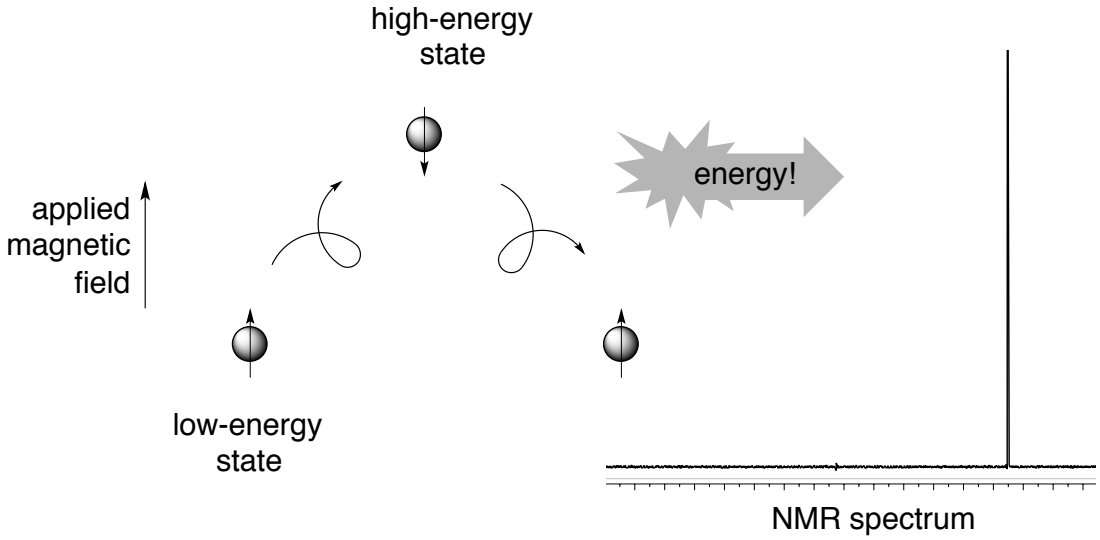


Figure 6.5. When magnetic nuclei drop from a high-energy state (where they're lined up *against* an external magnetic field) to a low-energy state, they release energy that can be translated by an NMR instrument into peaks on a "spectrum" (right); the position and shape of those peaks holds a lot of information about the molecule the nucleus is in.

It takes energy to stay in that state, though, so the nucleus will flip back down like a gymnast at the apex of a vault. On its descent, the nucleus releases a little burst of energy – exactly as much as it absorbed on the way up. An NMR instrument detects that energy, and turns it into a little spike amidst a hum of noise.

Just detecting little packets of energy from gymnastic nuclei wouldn't be all that informative on its own. NMR is so useful because the amount of energy it takes to somersault that nucleus is exquisitely sensitive to what the molecule around it looks like. Every nucleus in a molecule requires a different amount of energy. Blast a sample of

molecules with a whole bunch of radio frequencies at once (sort of like tuning your radio to all the stations at the same time) and one of those frequencies will be just right for a particular nucleus – flip! – and then another – flip! – and then another.

All those blips add up to a kind of magnetic signature. Chemists have been doing this for a long time, correlating the patterns made by these magnetic nuclei with molecular structures. Rhodium and phosphorus both belong to this class of "magnetically-active" molecules, along with protons. So our catalyst, whose business end both rhodium *and* phosphorus, and has plenty of protons, is set up perfectly for analysis by NMR. (The more magnetically-active nuclei are around, the more information you get, because when there are other magnetic nuclei nearby, they interact with their neighbors, doubling their peaks or giving them little satellites.) This means that we have direct access to a lot of information about our catalyst.

My job was to find out more about how hydroformylation happened. Why were the branched aldehydes formed so much faster than the linear ones? All I had to do was to add the starting materials to the catalyst – at low enough temperatures that everything slowed down a little – and use NMR to catch them in the act of joining together, seeing what combinations form.

It's a complicated reaction. The molecular dance that rhodium does to turn the starting materials into aldehydes has seven separate steps, with subtle variations for each possible product. The work in this thesis opens only a very small window into this process. It's not enough to tell us why our particular catalyst is so effective. Progress in science is incremental – it takes years to piece together a robust understanding of a

chemical process, let alone use that understanding to design an even better one. But in the meantime, it's just fun to try to figure out how things work.