

Zen and the Art of Molecule Making

On the essence and essentiality of chemistry and chemical thinking

Leif Sieben Oh, how weird is chemistry. – An adorably eclectic suite of disciplines actuated by a nearly equally eclectic collection of adepts. But what is chemistry and what is the meaning of chemical thinking? In essence, what is the way in which insight moves from nature to the chemist? An exercise in the *Verständnis vom Verstehen*.

I think organic chemistry is a scam: you try to explain a 90 % selectivity by covering 70 % of the cases while guessing would have given you the right answer 50 % of the time anyway.

A student of OC III

There are no models in chemistry.

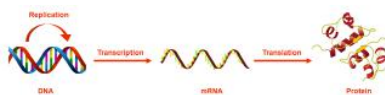
Granted, there are building sets for molecules which sometimes get called by this name. But models, in the way a physicist, data scientist, biologist or even philosopher of science would understand them, are peculiarly rare in chemistry. The essence of chemistry lies in the **making and breaking of bonds**, the transformation of matter in the laboratory and the description, explanation and prediction thereof. Essentially, chemistry is the art of molecule making.

What is missing, is this kind of fine-grained, predictive and yet sufficiently abstract kind of model that a physicist might use while describing the motion of a marble down a

slanted piece of wood with an inclination α . The physicist makes a number of assumptions:

1. The marble has a mass m with no extension (point mass).
2. The marble moves frictionless.
3. The piece of wood is stationary.
4. The electron moves in response to the gravitational force $m \cdot g \cdot \cos \alpha$.
5. ...

With these assumptions, the physicist can **make predictions** about the marble (e. g. How fast does the marble move? Where does it end up? etc.), which may then be **tested experimentally**. Biologists too have a vast number of such intellectual tools at their disposal: the central dogma of biology for example, which posits that genetic information moves from DNA to mRNA (transcription) and from mRNA to amino acids and proteins (translation)^[1].



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The model is how we understand the role that these various molecules play in a cell. It suggests a **functionality for these three components**. This might appear trivial but imagine an alien seeing a prokaryotic cell for the very first time. The alien has perfect analytical techniques at its disposal, but no prior knowledge. When the alien cuts open the cell, it will find a dense and rich soup of chemicals. What the alien will not find is any relation between them: is the cell-wall assembled from carbohydrates? Do the ATP kinases regulate the lipid concentrations? Like **a road map from which one has removed all roads**, the alien only sees **places unconnected** with each other.

The process of modelling gives meaning to this relation-less stream of molecules. It **reduces the complexity, always at the cost of precision**, but enlightens the function and necessity of the components involved. To calculate the path of a marble down a slanted piece of wood without a model is impossible: it would require knowing the exact shape of the marble down to the atom, the perturbation of the gravitational field that its movement would have, one would have to predict any friction between any atom of the marble and any atom of the wood to such a **degree of precision that Heisenberg's uncertainty would get in the way** and so and so forth. To predict with

perfect precision, i. e. absolute certainty, the path of the marble would **require complete (nearly infinite) knowledge**, knowing everything that is governed by the laws of physics, more probably than would even be allowed by these very laws themselves.

Teaching Me Softly

You would find it hard to find examples of this type of thinking in chemistry. But it is not fully true to refute their existence either, they are just often so fundamental they become hard to see: the idea of valence electrons is based on Bohr's model of the atom for example. The same could be said of oxidation states or the age-old debate between inorganic chemists of classifying ligands as L and X or *anionic* and *neutral*^[2]. But chemists have the strange tendency to **think of models as pure formalities**, truths *by convention*. Indeed, the idea that matter genuinely consists of small particles called atoms remained a point of debate until around 1880 in the chemical community^[3]. Despite the fact that *everyone* accepted the **utility of the purported formalism**. To put this into context: John Dalton had first made this claim in 1804 based on a hypothesis by Democritus dating back to around 400 BCE.

For the longest time, atoms were just useful mnemonics to the chemist to remem-

ber the number of isomers. **To remember but not to explain.** Most of us would probably also consider oxidation states, valence electrons, tetrahedral carbons, six-membered chair transition states and so on as not much more than useful conventions. While these formalisms permeate our thinking – oxidation states are part of IUPAC nomenclature, chairs are so often invoked in chemistry when you take OC III you feel like half of organic chemistry goes through one (with the other rest going through a boat) – chemists are uniquely reluctant to credit them for what they are: models that have certain assumptions (read: limitations) that can (read: if applied correctly) **predict the outcomes of a reaction.**

Chemistry is soft theory^[4]. Nothing we get taught in class is without limitations, **no explanation without drawbacks**; one often feels like back in French class where for any rule learned, you seemed to find more exceptions than cases that followed it. Sometimes this bugs us: it feels like hubris calling oxidation states a model when so much of it depends on the assumptions we make, when it is **impossible to derive it from any more fundamental concept** in chemistry, when it is sometimes in outright contradiction to the rest of chemical theory. Surely, we would like for our models to be as consistent as they are for those

eggheads in the physics department. How nice it would be if we could derive coordination chemistry from Brønsted-Lowry acid equations just as we derive the quantum harmonic oscillator from the potential of a freely swinging pendulum.

With the advent of quantum mechanics, **chemistry inched towards this goal.** But no one in their right mind suggests that Schönflies point groups will one day predict the stereoselectivity of a Buchwald-Hartwig coupling. Many of the most consistent theories (and many of the most confident self-identifying “modellers” among us) are found in physical-chemistry. But it would be disingenuous to take this for the main stage of chemistry. What chemists have been, are and always will be most preoccupied with, is the making of molecules. Ultimately, what we care about are the **yields, reaction times, selectivities, solvents, conditions** and so forth that are *required for or lead to* the matter we desire.

The Mechanism is the Model

Perhaps this seeming absence of models in chemistry is not such a great mystery after all. They were right in front of our eyes from the beginning: **the mechanism is the model.** The way chemists understand their chemistry is by drawing a structure and filling in some arrows. There is nothing

more key to the way a chemist thinks than their mechanism. No discussion about the enantioselectivity of some organic reaction can take place before you know the mechanism. From the mechanism, we derive the transition state. From the mechanism, we derive side-products, reaction coordinates, potential energy surfaces, i. e. activation barriers, thermodynamic sinks, reaction intermediates and so on.

One of the most productive chemical discoveries of the 20th century, the Ziegler-Natta olefine polymerization, is an informative and mostly representative such example. Based on initial observations that chromium catalysts were active in the low-temperature polymerization of ethylene, first Ziegler and later Natta optimized the process for ethylene and then propylene conversion. Today, these two polymers make up the largest-volume commodity chemicals in the world. It is perhaps not fair to call the discovery entirely serendipitous, rather it was **based on systematic screening and careful observation** by the scientists involved (many more than those two listed in the reaction’s name) intended to solve a real-world problem. Yet neither Ziegler nor Natta were guided by any kind of prior theoretical inkling and there was certainly nothing like a preceding model to explain the results observed. First, the

molecule gets made, **only then do we concern ourselves with why it might exist.**

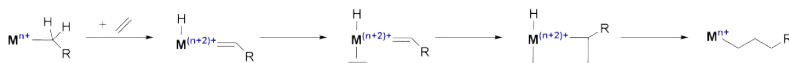
Indeed, the Ziegler-Natta catalysts, a combination of a group 4 metal (e. g. TiCl_4) and a Lewis acid organoaluminium (e. g. $\text{Al}(\text{Et})_3$), existed both in academia and in industry for decades before any consensus on the mechanism emerged. Notably, this **did not keep the chemical community from optimizing** the various aspects of the process. By the time Ziegler and Natta received their Nobel prize in 1963, two main mechanisms were proposed. One based on a metallacyclobutane transition state (Cossee-Arlman) and one based on full cleavage of the α C-H bond (Green-Rooney)^[5].

The Green-Rooney mechanism is a good example of a model that indeed explains most aspects of the mechanism – the products found, aspects of the kinetics, etc. – but is itself **entirely in contradiction with the rest of chemistry.** TiCl_4 as a d^0 metal cannot be oxidized to form a $\text{M}^{n+2}=\text{CH}_2$ bond. The Cossee-Arlman mechanism on the other hand could not explain why a kinetic isotope effect for the α hydrogen was observed. If no C – H bond is broken in the Cossee-Arlman mechanism, how could a substitution with a deuterium change the rate? The ultimate resolution of the problem came by invoking an α agostic inter-

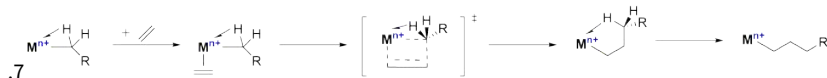
Cossee-Arlman



Green-Rooney



Modified Cossee-Arlman



action between the alkyl and the metal. The agostic interaction is the reason for the kinetic isotope effect and is needed to weaken the adjacent M – C bond. The transition state however looks much closer to the original Cossee-Arlman one and can thus also happen for d^0 metals.

What is interesting for us is not so much the actual mechanistic resolution of the problem but *what* such a discussion was based on and *why* it preoccupied the literature in the first place: The mechanism needed to explain **which reactants, transformed under which conditions to what products**. We may collectively refer to this as the *reactivity* of a reaction: its scope, its conditions and its product distribution. Green-Rooney could not explain why the known catalysts

were active, it was actually in direct contradiction to the results. Cossee-Arlman could not explain the kinetics (i. e. the kinetic isotope effect) and thus the yield and – because we are dealing with polymerization¹ – also what length of polymers one obtains. The final mechanism both explains why olefines are involved in the reaction and suggests why such a process can occur at low-temperatures (the α agostic interaction weakens the M – C bond). The mechanism too is nothing but **the set of assumptions we make about the reaction to predict its reactivity**. Such are the models in chemistry.

It is by the mechanism that we attempt to explain chemistry. It is the first thing that gets demanded when a new reaction is put

¹ Think Anderson-Schulz-Flory distribution.

forth. Any student in an organic chemistry Praktikum will know the deep existential angst of being asked by their assistant to draw up a mechanism for a reaction that one has never heard about. With the mechanism we try to understand and ultimately transform our chemistry: we optimize for solvents and reaction times, we find new ways to **increase or diversify selectivity, we discover reactions by analogy**. But the mechanism does not only shape our chemistry but it shapes us too.

The distance between the chemist and the gold-making alchemist at a medieval fair is about the same as between a tabloid astrologist and Buzz Aldrin². There is no scientific endeavour imaginable without the **constant attempt to make sense of the results** obtained. There is **no science without model**. But there are many models that are very much unscientific. Just ask any business student/aspiring consultant: they know a surprising number of them by heart.

Arabic alchemists of the 8th century AD used tables to drive their research: four columns, one for each of the four qualities of matter (hot, dry, wet, cold), and seven rows for the seven intensities these qualities can take. They then placed the 28 letters of the Arabic alphabet onto this grid.

² The second astronaut to step onto the Moon

The word lead (*usrub*) for example is written with four letters: *alif, sin, ra and ba*. We learn that lead is thus associated with hot in the highest grade and dry in the fourth grade and so on^[6].

You might consider such a model ridiculous. You would not be wrong. But one must beg the question of **how much more absurd it is to sacrifice four years of one's most productive age to get to the total synthesis of some microbial antibiotic**^[7]. Just remember that the excitement of getting a yield for some intermediary reaction from 80 % to 85 % is a fascination shared by few outside of a chemistry department.

The power of the model is not only in explaining what we find, not only in **predicting** what we will find. The model motivates us to search at all. The alchemist did not just stumble around in their private laboratory, mixing substances at will, hoping to find the Philosopher's stone. An impressive amount of thought went into this labour. How else should anyone have the motivation to get up in the morning and attempt over and over again to try and create this nearly all-powerful matter by means that can so often appear nearly all-futile. This struggle is true for the alchemist trying to make gold out of lead with a crucible; as much as for the synthetic chemist making

life-saving drugs via column chromatography.

A Zen Buddhist's Advice for Total Synthesis

But models, mechanisms in particular, **can sometimes be limiting too**. Just as the biologist could not make sense of the cell's molecular soup without understanding the role DNA, RNA and proteins play, no chemist could make sense of the bizarre instructions and unique combinations of molecules some experimental might ask of them. But we can get caught up in those mechanisms too. Just because our model gives a function, a reason for one component does not prove that **it could not have a different role too**. RNA is a messenger between DNA and proteins but it is also a vital part of the ribosome, a gene regulator, and takes part in the immune response. What RNA comes down to is just some atoms in a nitrogen base, a sugar and a couple phosphate groups. A cell is just a big collection of molecules after all. The lines we draw between them are very much human drawn. Any good Zen monk would teach you this too: it is **not so much reality that shapes your mind but your mind that shapes reality**. When you look out your window and make out perhaps a tree or a road or people, can you be really sure that they

are there? Could they not be an illusion perhaps by mirrors or perhaps by your mind? In brief, what reaches your eyes are not trees or a road or people, it is simply a **collection of photons that illicit some response**. That is at best what you can be truly sure of. All the rest is your interpretation, your **mind giving shape to this stream of perceptions**.

The 1974 book *Zen & the Art of Motorcycle Maintenance – An Inquiry into Values*^[8], which would go on to become America's most-sold book in philosophy ever, about a biochemistry student turned philosopher turned motorcycle enthusiast goes on about this in length. Robert M. Pirsig (himself once a student of chemistry) writes:

That's all the motorcycle is, a system of concepts worked out in steel. [...] I've noticed that people who have never worked with steel have trouble seeing this – that the motorcycle is primarily a mental phenomenon. They associate metal with given shapes – pipes, rods, girders, tools, parts – all of them fixed and inviolable, and think of it as primarily physical. But a person who does machining or foundry work or forge work or

welding sees 'steel' as having no shape at all. Steel can be any shape you want if you are skilled enough, and any shape but the one you want if you are not. [...] Steel has no more shape than this old pile of dirt on the engine here. These shapes are all out of someone's mind. [...] Hell, even the steel is out of someone's mind. There's no steel in nature. Anyone from the Bronze Age could have told you that. All nature has is a potential for steel. There's nothing else there. But what's 'potential'? That's also in someone's mind! ... Ghosts.

On a Serious Note

This is not to say that there is some vast untapped potential of chemical discovery to be accessed simply by considering more of chemical theory for what it is: a bunch of models. But unlike a formalism or a convention, a model is something to be taken seriously. There are **genuine formalisms in chemistry** and it would be nothing short of a **waste of time** to analyze our rococo-like IUPAC names with the same painstaking care that once Arabic alchemists applied to

theirs. But models are serious things and they are genuinely how we **make sense of nature in science**. They are never comprehensive, **not always reducible onto something more profound**, not even always in agreement with each other. But it is the best we can do if we are genuinely interested in tickling from nature her secrets.

Taking models seriously does not itself offer any new understanding. But by the quirks of human psychology, **genuinely believing something often motivates much bolder and much braver behaviour**. Perhaps more often than not taking our models seriously (also in teaching them!) would not so much provoke new insight as make us more conscious of our limitations. All too often those allegations of “formalism” (how Stalinist indeed) **do not lead to greater scepticism but to a near apotheosis** of the recipe: because when you only study with those examples you are given in the problem sets, the formalism seems better than perfect. It is only when we take things seriously, when we think them through until nothing wobbles anymore, when we go the very rim of our ideas that we understand what we truly know. One is reminded of the old joke about the farmer who would never eat his own vegetables because “when one only eats vegetables, where does the stuff come from to

make your bones?”. The farmer then carries on with his labour and tills the field on his strong oxen with his sturdy and all vegetable-made bones.

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