

Long Live the Intermediate!

Roald Hoffmann

IN THE FORTHCOMING U.S. presidential and congressional campaigns, I guarantee that we will hear, and not just once, the stock characterization of a candidate as “a catalyst for change.” You might think we’d weary of this phrase, but the part of our psyche where hope eternally resides will not let us do so. Note that this expression invokes catalysis, one of the few chemical concepts that enter common parlance. As agents of transformation and profit, catalysts capture the collective imagination. But there is an equally deserving alternative for our attention: the reaction intermediate.

Making a Go of It

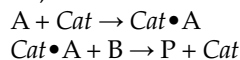
Suppose A and B are molecules that, according to the strict dictates of thermodynamics, should react spontaneously to give a product we will call P. (P could be more than one molecule.) Technically, what I mean by “should react” is that the Gibbs energy—that marvelous combination of enthalpy and entropy—decreases as A and B are transformed into P. In other words, the reaction liberates energy and, like water flowing downhill, should proceed spontaneously.

Often, however, the reaction does not go, even if we put in a moderate amount of energy via heat. The reason it doesn’t go is that the eventual payoff—the Gibbs energy that is waiting, so to speak, to be released in the reaction—is just not available to gently colliding molecules in thermal equilibrium. The reaction has an activation energy (a Gibbs energy, too), a hill that must be climbed before the energy that is set free in the reaction becomes available. The hill is represented in the top half of the figure at right. At ambient temperature and pressure, only an infinitesimal number of molecules

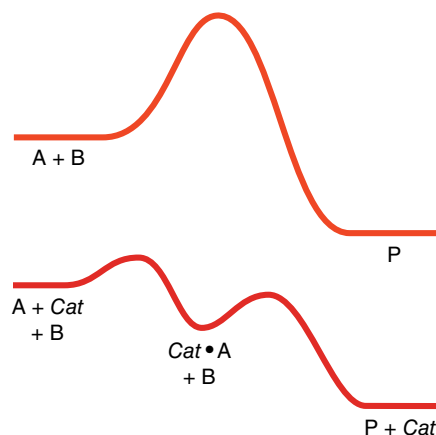
*What’s in between
in a reaction matters
just as much as what
sets it off*

acquire sufficient energy in collisions with each other to get over that hill. Tough on you, if you want the reaction to go, but too often true.

Here’s where the catalyst comes in. The sequence of reactions that transpires, called the mechanism of the reaction, is given below. *Cat* stands for the catalyst and *Cat•A* for another molecule, the reaction intermediate.



The energy profile that accompanies this sequence of two reactions, shown



Catalysts make reactions go more readily. Here, each red curve represents energy consumed and released when molecules A and B react to produce product P. The uncatalyzed reaction (top) requires considerable energy input to get over the “activation energy,” the hill between reactants and products. In the catalyzed reaction (bottom), the catalyst interacts with A, producing a reaction intermediate (*Cat•A*) that also goes on to P, but with lower energy input.

in the bottom half of the figure, is fundamentally different from that of the uncatalyzed reaction. Now the barriers to each reaction are much smaller—which means that one has found a good catalyst. The energy available at ambient temperature, or from slight heating, is now sufficient to coax the reacting molecules over both small hills. The reaction goes readily.

The catalyst gets intimately involved in the reaction and is regenerated. It vanishes, to reappear. Resurrected, it is ready, in principle, to escort another pair of molecules (one of A and one of B) through the reaction. It looks as though it could do so forever, as if one molecule of a catalyst could take, say, a tablespoon or a beakerful of matter through the paces. In reality, no catalyst does so well. There are molecular seductions or dead ends lurking in the solution. They “spoil” the catalyst, sour it, poison the process. One way or another, they pull the catalyst away from its appointed rounds. In the trade, a *turnover number*—the number of reactant molecules guided through the reaction by one catalyst molecule—is a measure of its efficiency. Turnover numbers of 10^5 are pretty good in the real world, perhaps good enough to build a factory on. The greater the turnover number, the more expensive you can afford the catalyst to be.

A Coin Has Two Sides

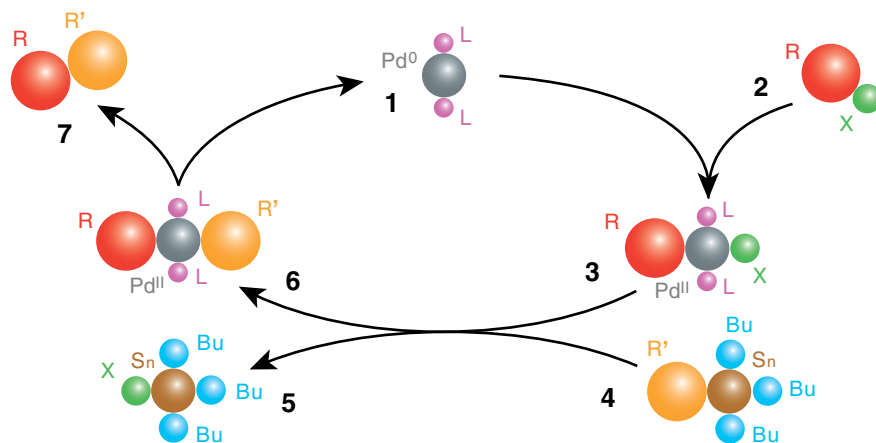
The catalyst, however, is hardly all there is to the story. As the reaction mechanism above mandates, the catalyst has a partner, often unseen. This elusive entity is the reaction intermediate *Cat•A*. Actually, “partner” is the wrong word; you can’t have one without the other. While the catalyst gets involved and is regenerated, the reaction intermediate does the reverse. It was not there when the reaction began. It is generated and then disappears, to reappear again in the next cycle.

Roald Hoffmann is Frank H. T. Rhodes Professor of Humane Letters, Emeritus, at Cornell University. Address: Baker Laboratory, Cornell University, Ithaca, NY 14853-1301. E-mail: rh34@cornell.edu

This pairing of catalyst and intermediate is a feature of all catalytic cycles, from the simple example on the previous page to the more complicated real-world reactions. There's nothing weird in these fleeting transformations—no philosopher's stone, no action at a distance—just plain, good old chemistry. The figure at right, for example, shows a very useful reaction that builds carbon-carbon bonds in complex organic molecules, such as one might need to make a pharmaceutical. The reaction is known as the Stille coupling, named for its originator, the late John Stille. Molecule 1 is the catalyst here, a compound that consists of palladium (Pd) in its reactive, zero-oxidation state, with ligands (L) attached. Molecule 2 is the reagent, RX, where R is an organic group such as CH₃ or C₆H₅, and X is a halogen atom such as fluorine. This reagent adds to the catalyst in a reaction called an oxidative addition, in which Pd donates two electrons to form bonds with both R and X. Thus is generated 3, an intermediate, actually the first of two in this cycle.

The intermediate, in turn, reacts with 4, a compound composed of tin (Sn), three butyl groups (Bu) and another organic group (R'). In this reaction, the X on Pd is traded for R', generating two products. One is 5, in a sense a by-product. The other is 6, a second intermediate that has both R and R' attached to the Pd. It expels the twain in a reaction called a reductive elimination. The net result is that the two organic groups, R and R', are linked together by a new carbon-carbon bond, 7. That is the aim of the reaction, the thing that makes it useful. At the same time, the catalyst is regenerated. Reactions quite similar to this were rewarded with the 2010 Nobel Prize in Chemistry.

The Stille coupling is an example of homogeneous catalysis: All reactions take place in a solution. The pairing of catalyst and intermediate also happens in heterogeneous catalysis, in which reactions take place on metal particles or on reactive centers bound to solid grains. For example, metal surfaces that break apart hydrogen and nitrogen molecules (H₂ and N₂) and bind the separated atoms to the surface are the intermediates in what is perhaps the single most important catalytic industrial process of our world, the Haber-Bosch process. That reaction, illustrated at the bottom of the following page, is responsible for combining hydrogen



The Stille coupling is a series of reactions that forms new carbon-carbon links in complex organic molecules. A catalytic palladium compound (1) facilitates the bonding of two organic groups (red and orange balls) that start out on two separate molecules (2 and 4) but end up together (7). In the process, the reaction cycle generates and consumes two intermediates (3 and 6).

gas and abundant atmospheric nitrogen into a biologically and chemically useful molecule, ammonia (NH₃). Half of the many nitrogen atoms in your body have seen the inside of a factory, have visited the small metal particles that catalyze this incredibly successful reaction.

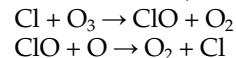
Intermediates are just as ubiquitous in our bodies, in the still more successful biochemical reactions crafted by evolution. Here, the catalysts are enzymes—the ever-so-efficient molecules (proteins themselves) that facilitate, for example, the removal of amino acids, one by one, from ingested proteins. During each step, the enzyme's active site binds the substrate, temporarily forming an intermediate.

They're Hiding

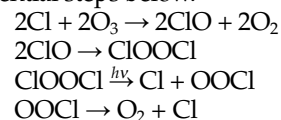
One reason intermediates don't get much press is that they are, well, intermediate. They decompose easily. They are not around in large concentrations, or for very long. They are fleeting. You have to be quick and handy to catch a glimpse of them, say, by observing a characteristic spectrum. Your method has to be exquisitely sensitive, for in principle the better the catalyst—the greater its turnover number—the less chance you will have to observe the intermediates. The title of this column may evoke a small smile from the catalytic chemist, who knows that if you have a long-lived intermediate, you are unlikely to have a good catalyst.

Enough talk; we need an illustration of the detection of an intermediate. In this context, I cannot resist showing one of the greatest scientific images of all time: the smoking gun in our understanding of how chlorofluorocarbons

cause the ozone hole. It begins when chlorofluorocarbons, inert and harmless at sea level, are photolyzed in the stratosphere to give not one but a series of chlorine reservoirs: Cl₂, HOCl, ClNO₂. These compounds are adsorbed on ice crystals in polar clouds and then photolyzed by spring sunlight, easily releasing Cl atoms. These atoms then initiate a catalytic chain that decomposes ozone. The simplest possible mechanism for that decomposition, first proposed in the 1970s, is as follows:



But nothing is simple in this world (except for our minds when we listen to those political ads), and this mechanism is no exception. As musician Joe South wrote, "I never promised you a rose garden." The sequence above requires oxygen atoms, which, as it turns out, are scarce in the Antarctic stratosphere. The actual course of events is more complicated, and includes the four essential steps below.



The overall reaction for the simpler mechanism, then, is O₃ + O → 2O₂; for the second sequence, it is 2O₃ $\xrightarrow{h\nu}$ 3O₂, where hν represents energy from sunlight. In both mechanisms, Cl atoms are the catalyst and ClO is an intermediate. Like the Stille coupling, the second mechanism has multiple intermediates, also including ClOOC and OOCl.

The very reactive intermediate ClO is not something you can pull off the shelf. In the 1980s a spectroscopic probe was created to detect the tiny amounts

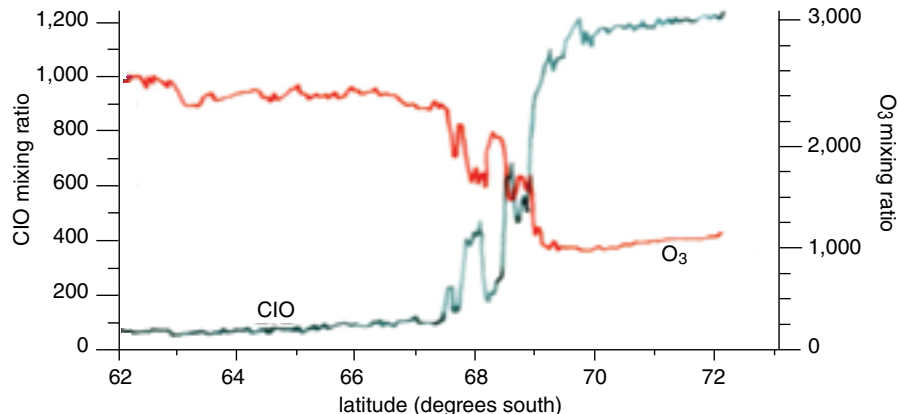
of ClO in the polar atmosphere. The probe was put on board a plane that took off in 1987 from Punta Arenas, at the southern tip of Chile, and flew at high altitude south toward the pole and into the ozone hole. The plane also carried a probe for ozone. The figure at right shows the resulting measurements. They demonstrate, ever so clearly, that the ozone concentration goes down (that's the hole!) just where the ClO concentration goes up. I hope you see the units of the ClO measurement (parts per trillion volume), to appreciate the experimental achievement here.

Characterizing a reaction intermediate is hard work—harder, I think, than finding a catalyst. Mind you, my catalytic chemist friends disagree. Their students struggle to discover new catalysts. But as an outsider, a theoretical chemist, when I look at the chemical literature, here is what I see: Reaction mechanisms, where intermediates are lurking, are easy to write down but often devilishly difficult to pin down. Into the establishment of mechanisms goes great experimental ingenuity in weighing the evidence from rates of reactions, isotope effects and the direct detection of intermediates. This is as true of reactions that are not catalytic as ones that are; few reactions proceed in one fell swoop, and most go through intricate sequences with fleeting intermediates galore.

As Lewis Carroll wrote in *The Hunting of the Snark*,

You may seek it with thimbles—
and seek it with care;
You may hunt it with forks and
hope;
You may threaten its life with a
railway-share;
You may charm it with smiles and
soap—

And you may hope that, even if you do not vanish, neither will your chemi-



A reaction intermediate was the smoking gun that confirmed the chemical mechanism that forms the ozone hole. By the mid-1980s, chlorofluorocarbons were the suspected culprits, and chemists had proposed that chlorine atoms might catalyze the destruction of ozone (O_3). Chlorine monoxide (ClO) was a putative reaction intermediate. To confirm that mechanism, airborne sensors measured the ClO concentration in parts per trillion volume (blue line) across a range of latitudes and revealed that it increased dramatically exactly where O_3 concentration (red line, parts per billion volume) decreased—that is, at the ozone hole. (Image courtesy of Jim Anderson.)

cal reputation, as has that of more than one unfortunate seeker. By comparison, finding the overall reaction and the catalyst seems simpler. In favoring the catalyst, I would say that we take the easy road in what we admire.

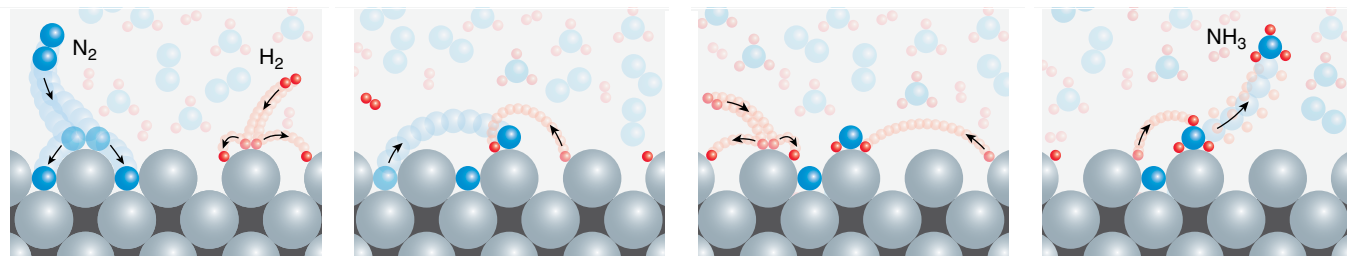
Of Myths and Money

The catalyst's hold on our imagination is not, of course, solely a matter of laziness. I see several reasons that it may fascinate us more than its paired reaction intermediate.

Magic: In the workings of a catalyst there seems to be something special, even mythological. The catalyst, often precious, is lost—and then returns. The phenomenology here connects with the archetypal cycles of the Earth, as expressed in our mythologies and religions. Think of Phoenix rising from the ashes, of Persephone's sojourn in Hades and her periodic return, of reincarnation, of resurrection. Indeed, it took some decades to move from the alchemical conception of catalysis in the 19th century to the mechanisms

we know today. Still, the wonder remains. A catalyst is magical, and loses none of its magic if we know how it works. How could a reaction intermediate compete? It is not resurrected; it just fades away. Its detection, no matter how ingenious, has at best the feeling of a satisfying detective story.

Lucre: Part of the wonder of catalysis—like that of alchemy in earlier centuries—is the promise of riches. If a catalyst can make go a desired yet recalcitrant reaction—a reaction that is essential for the production of a compound with a market—and if it makes that synthesis more efficient than that of competing companies, that catalyst is valuable. Most, if not all, industrial processes involve catalysis, and one tries to protect these compounds with patents. They are essential intellectual property. But I have a feeling that not every important catalyst is patented. Because small amounts of matter can be catalytic, and their action so specific, it may be simpler to keep the real catalyst as an unpatented trade secret—with the



The Haber-Bosch process produces a useful product, ammonia (NH_3), from hydrogen (H_2) and atmospheric nitrogen (N_2). A chemically modified iron surface (gray balls) catalyzes the reaction by splitting H_2 (red balls) and N_2 (blue balls) into individual atoms (first panel). The atoms on the surface then interact with each other to produce a series of reaction intermediates, NH and NH_2 (middle two panels). Finally, the desired product, NH_3 , is released from the metal surface (fourth panel).

attendant dangers of it being stolen, or worse, discovered independently and patented by a competitor. You can wait to find the intermediate after you discover and patent the catalyst. Actually, could you even patent an intermediate if you wanted to?

Serving humanity: Humans are moved by selfishness and altruism both. The fact that half of the nitrogen atoms in our bodies have seen the inside of a Haber-Bosch factory is not only certification of profit for the companies involved; it is also a statement that twice as many people are alive today as would be if there were no such factories producing ammonia fertilizer. Organic agriculture could take up some of the difference, but in my opinion, not close to what is needed. Catalysis feeds the world.

We usually think of catalysts as good because they give us more of what we want (such as fertilizer). But the world doesn't care for our values. In its natural or unnatural processes, it catalyzes reactions we don't want (decomposing ozone, spoiling meat), just as often as those we do.

Privileging the Intermediate

Perhaps we value the catalyst because it comes first: Could it be that you can't have a reaction intermediate without first having a catalyst? I don't think so. In fact, the clue that catalysis is at work is often simply the rate of reaction. A transformation that we thought would be slow in fact goes like a shot. In such reactions one looks as often for the reaction intermediate as for the catalyst.

The intellectual bonus of finding a reaction intermediate is that it immediately suggests what the catalyst is, and may, in fact, give you the reaction mechanism in one fell swoop. If you find a catalyst, as valuable as that discovery may be, it does not give you the mechanism. It only provides you with the impetus to write down alternative mechanisms for the way the catalyst might tangle with the reactant.

In recent times, people have found new ways to look for catalysts, ways that focus on the intermediates. One such approach is the *de novo* design of enzymes: Pick a reaction you want to have happen, sculpt the essentials of the active site (which, together with the substrate, forms the intermediate) and fine-tune the rest of the protein. Another approach is directed evolution, in which libraries of potential catalysts

(not only enzymes) are generated and tested for their ability to catalyze a reaction. Their ability to destabilize reaction intermediates—a way to higher turnover numbers—can be probed, remarkably, by mass spectrometry. Only the most effective versions are selected for further refinement.

Each of these approaches—and there are many, for the field is supremely active—deserves an essay on its own. Here, let me provide two older examples, to which I was guided by two of my colleagues, Brian Crane and Geoff Coates, both great hunters of catalysts.

An intermediate found first. It's hard to turn back the clock in a field as dynamic as molecular biology. But in the mid-1950s the ribosome was just beginning to be seen, and the details of protein synthesis were unknown. In a critical experiment, biochemists Mahlon Hoagland and Paul Zamecnik discovered a reaction intermediate involved in protein synthesis: the aminoacyl adenylates, amino acids that have been "activated" in a reaction with adenosine triphosphate (ATP). Within a year of the discovery, multiple research groups had begun to describe the enzymes responsible for that activation.

The same enzymes turn out to catalyze a second reaction, too: the addition of the activated amino acid to a transfer RNA (tRNA). The latter compound shuttles its specific amino acid component to the ribosome, where it is added to a growing chain of amino acids during protein synthesis. The enzymes in question are now well known as aminoacyl tRNA synthetases. They were discovered because the relevant intermediates in the activation of amino acids were found first. Indeed, aminoacyl adenylate intermediates are so unstable, so easily added to tRNAs, that they are difficult to isolate in the presence of tRNA.

An intermediate that became a catalyst. Like all real stories, that of Karl Ziegler's remarkable development of ethylene polymerization catalysts is not a simple one. Ziegler and his coworkers were studying the reaction of lithium aluminum hydride (LiAlH_4) with ethylene, a two-carbon compound. Their products were longer-chain hydrocarbons, 4 to 12 carbons long. From the LiAlH_4 reagent they moved to aluminum hydride (AlH_3), which also catalyzed the reaction. But then Ziegler discovered that a reaction intermediate in the AlH_3 reaction was triethylaluminum,

$\text{Al}(\text{CH}_2\text{CH}_3)_3$. This compound, which could be made independently, was an even better catalyst for polymerizing ethylene. Substantial pressure was still required to make the polymerization go; the process was much improved by the participation of titanium chloride (TiCl_4). To this day, small mysteries remain in the details of this reaction, but a world without polyethylene plastics is hard to imagine.

Equal Time

To return to the metaphor of creating social change, I would suggest that real change is not the product of a single catalytic substance, like the personality of a leader, or a formula that imposes or removes a tax. Change—be it of American attitudes toward conserving electricity, or abandoning racial or gender stereotypes—will come about through many small actions by individuals. In a way, these are the intermediates.

Perhaps I have sought a little too hard to privilege the intermediate. A fairer statement of the realities of chemistry might be the following: Finding a catalyst gets you chemical action (and potential profit); finding a reaction intermediate gets you the mechanism. I guess that as a theorist, I'm a man of understanding, not an action hero. Or maybe, just maybe, in rooting for equal time for reaction intermediates, I'm just for the molecules less hailed, the ones less capable of evoking the mythological structures that reside in our minds.

Acknowledgments

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