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Mediated Electroorganic Oxidations: Applications in Pharmaceutical Building Block Synthesis and Biomass Depolymerization

By

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Chapter 1: Control is the Goal! Using Electricity and Mediators to Make Molecules

This work is an introductory chapter for a general audience.

I wrote this chapter to describe the context and some findings of my doctoral research to my family and friends who are part of a broad, non-specialist audience because I want to share my science with everyone in my life. I would like to thank the Wisconsin Initiative for Science Literacy (WISL) at UW-Madison for providing this platform, and for sponsoring and supporting the creation of this chapter. I am especially grateful to Professor Bassam Shakhashiri, Elizabeth Reynolds, and Cayce Osborne for their valuable feedback and encouragement.

It's hard to imagine a world without electricity; we use it to power everything from smart watches to city lights. We're also familiar with the idea of storing electrical energy in batteries. But did you know that electricity is also used to make the chemicals found in everyday items?! **The field of electrochemistry**, a compound word formed from "electricity" and "chemistry", **uses electrical energy to drive chemical reactions that do not happen spontaneously**. Electricity is the movement of small, negatively charged bits of energy called electrons, and the atoms that make up molecules are made of electrons and central positively charged bits called protons. In Figure 1.1 the electrons are shown as little yellow balls joined with their best friend, the bigger gray proton ball. The bonds between atoms in a molecule are made of the shared electrons. The yellow electron balls in Figure 1.1 are also joined with a big red square, which represents all the other atoms and bonds that make up the rest of the molecule.

When you think of chemical reactions, you probably imagine a scientist adding a liquid to another liquid or powder in a glass container. Electrochemical reactions are similar, but they need a little something extra to conduct electricity through liquid. Two pieces of electrically conductive material like metal or graphite are added into the container liquid and chemicals. The ends of the conductive pieces sticking out of the solution are attached to a piece of equipment that modulates the electricity coming out of a typical wall socket to the amount of electrical energy needed for the reaction. Both pieces of conductive material are needed to conduct an electrochemical reaction, like a battery needs both a positive and negative end, but often the electrochemical reaction of interest is only occurring at one of the pieces and any reactions at the other piece can largely be ignored. Figure 1.1 shows just the one piece of conductive material as a big gray bar attached to the source of electricity, although we don't actually use lightning.

Electrical energy applied to these conductive pieces can directly add or remove one or more electrons from a target molecule. Figure 1.1 shows one electron being removed from the red block molecules at the conductive surface. Notice that the proton is not removed with its electron best friend. These "direct" electrochemistry reactions have been around since the 1800's and are performed on large scale by chemical companies in the process of making Nylon, a plastic used in swimsuits and carpets**. The direct transfer of a single electron from most carbon-based molecules incurs a high energetic cost** because electrons and their atomic proton counterparts are happier and more stable moving together as the element hydrogen (one electron and one proton) or the negatively charged version known as a hydride (two electrons and one proton). Figure 1.1 shows that after direct electrochemical removal of an electron the lonely proton (gray ball) leaves the molecule (red square) quickly afterwards.

The high energetic cost means that a relatively large amount of electrical energy, measured as voltage, is required to remove or add a single electron without its proton friend to or from a molecule. For simple molecules containing few atoms and bonds, like the molecule used for making Nylon, direct electrochemistry works well because it doesn't matter how much energy you use to separate the electron and proton couple. Imagine the electrical energy as a big sledgehammer. Using the sledgehammer to pound one nail into a simple wooden board might be overkill, but it’ll work. Now imagine trying to pound just one nail in the center of a board full of nails using just the sledgehammer and it becomes clear that the high voltage required by direct electrochemistry fails for selective addition or removal of a desired electron from more complex molecules.

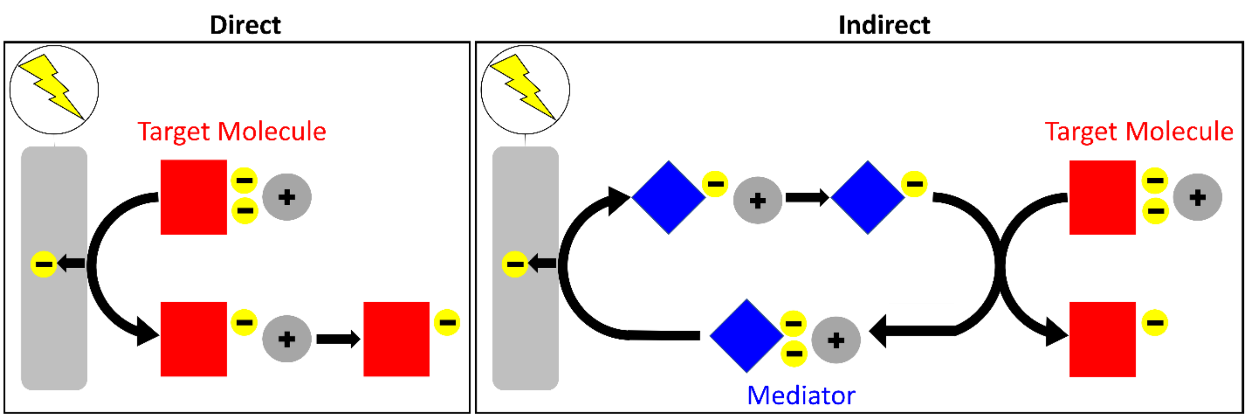
Scientists over the last 40 years worked hard to overcome the limitations of direct electrochemistry and find a toolbox that has a smaller hammer. They searched for, and found, a handful of relatively simple molecules that were able to undergo direct electron transfer at low voltages. This small group of molecules are not themselves valuable as target molecules and cannot be converted into new or valuable chemicals. However, some of these special molecules could *also* transfer one or more electrons and its coupled proton together from interesting target molecules. This subset of specialized molecules is known as proton-coupled electron-transfer mediators and are shown as blue diamonds in Figure 1.1.

The use of mediators has been used to develop an entirely new type of electrochemistry! The full process of transferring an electron from the target molecule (red square) to the mediator (blue diamond) and then to the electrical source shown in Figure 1.1 is aptly named “indirect” or “mediated” electrochemistry. Figure 1.1 also shows that after direct electrochemistry removes an electron from the mediator (blue square), it transfers an electron and proton from the target molecule (red square) and regenerates the initial form of the mediator. Therefore, the mediator molecule is not used up during the reaction.

Indirect reactions employing proton-coupled electron-transfer mediators can operate at much lower energy than direct electrochemistry, which is like trading that big sledgehammer for a standard claw hammer. The voltage hammer is small and only sufficient to add or remove electrons from the mediator. The mediator is then able to transfer only one set of coupled electrons and protons from the target molecule, even if the target molecule is complex and contains many types of atoms and bonds. Furthermore, molecules are also kind of like puzzle pieces in that they have a specific shape that fits well with only some parts of other molecules. Both traits enable mediators to be selective in the electrons and protons they remove from complex molecules.

The selectivity of indirect reactions can be used to enable new types of chemical reactions.

Figure Error! No text of specified style in document.**.1.** The direct electrochemical removal of an electron (yellow circle) from a target molecule (red square) and indirect removal an electron (yellow circle) and proton (gray circle) using a mediator (blue diamond).



Example 1

Let's examine an example from my own research. Science is rarely carried out without the collaboration and support of other scientists. I conducted this research under the mentorship of my coworker Alastair Lennox. The research that we completed together showcases the power of electrochemical mediators for making molecules that could be used in the discovery of new drugs.

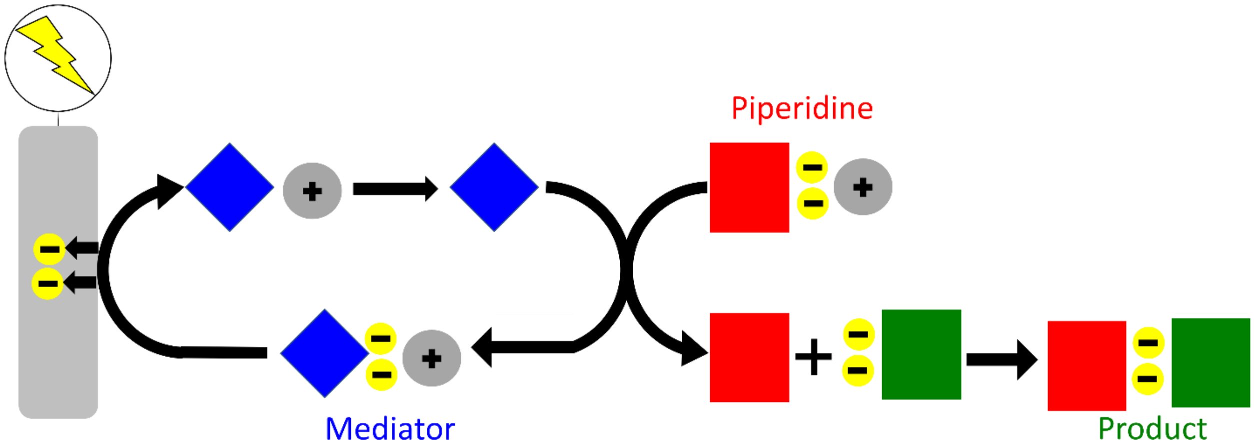
Pharmaceutical chemists create the large and very complex molecules typically used for drugs by sequentially adding molecules to one small molecule in the same way that small pieces are glued together to build a model airplane. Piperidine is a simple molecule that is often found as part of the larger molecular structure of many commercial drugs. Removing electrons and a proton from piperidine allows another molecule to be attached to piperidine. Since this kind of attachment to piperidine may need to occur later in the drug building process, the ability to remove electrons from only the piperidine part of a complex molecule is highly desirable and may enable the design of new life-saving drugs.

To start this project, the first thing that we did was throw out the sledgehammer. Piperidine undergoes direct electrochemical removal of electrons using approximately 0.85 volts of electrical energy. Other parts of complex drug-like molecules that may be found alongside piperidine could *also* undergo electron transfer at or around this voltage. Using a high voltage sledgehammer to remove electrons from piperidine may affect the other parts of the molecule capable of undergoing electron transfer. Remember all those nails in the board? These other parts may be crucial to how the drug works in the body, so we wanted a way to lower the voltage and facilitate the selective removal of electrons from piperidine in complex molecules.

A mediator seemed like it might be perfect for this job! First, we required a mediator that undergoes direct electrochemical removal of electrons at voltages lower than any part of the target piperidine-containing molecules. We selected four similar mediators with slightly different molecular structures labeled as **1-4** in Table 1 that we suspected, based on work done by other scientists, could undergo direct electrochemical transfer of electrons at low voltages. We added each mediator to some liquid, inserted, the conductive pieces into the liquid, and measured the voltage needed to remove electrons from each of the four mediators. Direct electron transfer occurred between 0.19 and 0.43 volts for all the mediators. The mediator that undergoes direct electron transfer at the lowest voltages (as shown in Table 1) was the most desirable because any part of a target molecule with a higher energetic requirement for direct electron transfer wouldn't be affected. Basically, the tinier the voltage hammer, the easier it is to hit only the mediator. But, we couldn't just pick a mediator based on voltage. The mediator also must successfully transfer two electrons and a proton (a hydride) from a simple piperidine-containing molecule.

Unlike voltage, which can be measured directly, the hydride transfer reaction between the mediator and piperidine had to be measured indirectly. Since hydride transfer enables the attachment of another molecule (green square) to piperidine (red square), we simply measured the amount of conjoined product (attached red and green squares) produced from the indirect electrochemical reaction with each mediator in Table 1.1. An indirect reaction that converted all the piperidine to the conjoined product (100%) would indicate that the mediator is perfectly successful for indirect transfer from piperidine. Mediators **2** and **3** give only small amounts of product. These mediators have a molecular structure that likely does not fit well with piperidine, like two puzzle pieces that don't match. Mediator **1** results in the formation of less product than mediator **4**, but it also requires much less energy for direct electron transfer.

Table 1.1. Mediator comparison of required voltage and amount of product for indirect electrochemistry of piperidine



	Voltage	Product
Mediator 1	0.19	54
Mediator 2	0.23	10
Mediator 3	0.32	24
Mediator 4	0.43	81

We chose to test mediator **1** for the indirect proton-coupled electron-transfer of more complex piperidine-containing molecules. Many different piperidine-containing molecules were able to be converted to the desired product, meaning that the only part of the molecule primarily engaging in electron transfer was piperidine! A method for making these products had never been reported before, we published a paper in a scientific journal letting other scientists know that **mediators enable the production of molecules that could be useful for making new drugs**.

Example 2

This example from my research showcases the power of electrochemical mediators for facilitating the production of valuable chemicals from wood.

The part of wood we're most familiar with is the part of wood used to make paper. During the paper making process, the rest of the wood is removed and burned to generate the heat needed for processing more wood into paper. One of these "waste" components is an incredibly complex molecule called lignin, which is made up of many smaller molecules linked together into a long chain. Imagine lignin as a series of blocks each tied together with string. Chemically cutting certain ties between the molecules has been shown by other researchers to produce many valuable molecules that may replace chemicals typically derived from non-renewable fossil fuels.

Unfortunately, the chemical process of separating lignin from the part of wood used for paper damages the lignin linkages and prevents them from being cut, which is akin to taking all the strings and tying the blocks together in one big knot. The removal of two electrons and one proton from lignin could protect the lignin from being damaged during the wood separation process and will facilitate the subsequent chemical severing of the linkages in isolated lignin. However, the part of wood used for paper making can also undergo electron transfer. Once this occurs, it can no longer be used for paper making. Making just the molecules you want, and few or none of the ones you don't, is one of the biggest challenges in chemistry.

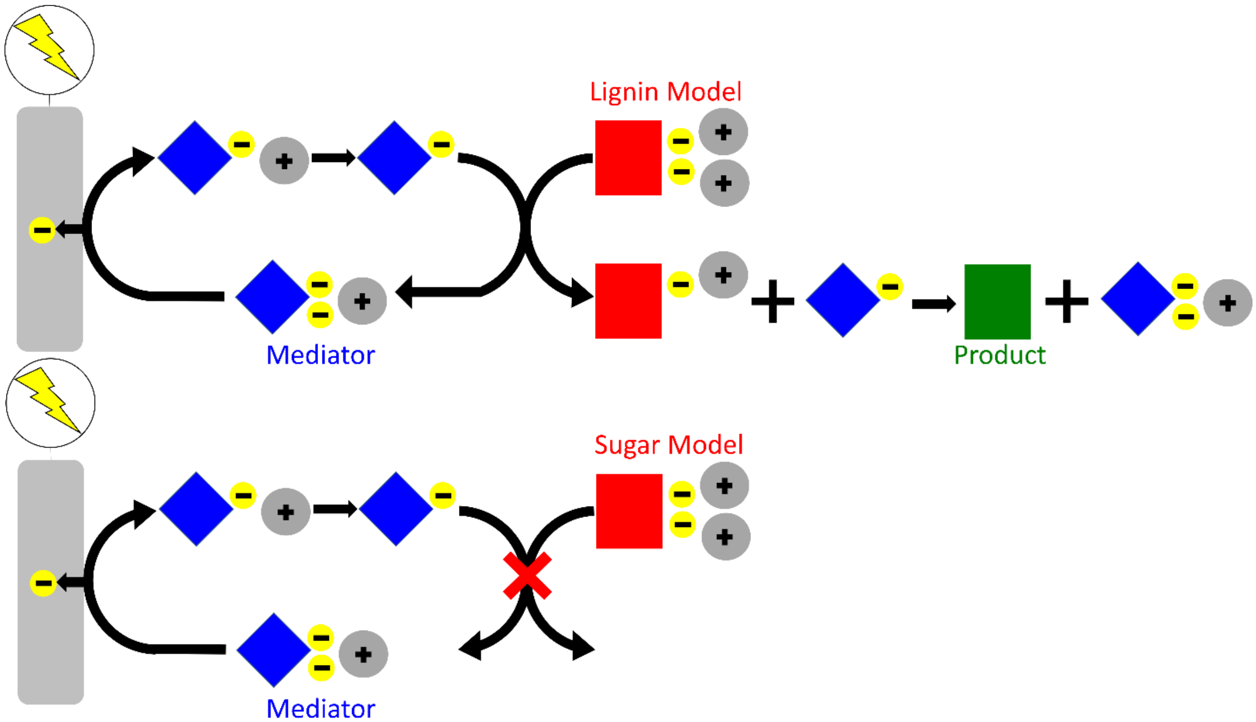
Wood is an amalgamation of very complex molecules, and the analysis of such a complex mixture is… complex. Since we knew that we may have to conduct many reactions and analyze the products of those many reactions, we decided to start with reactions using simplified molecules, known as models, that would likely react similarly to the real thing. The simplified lignin model molecule is a type of alcohol, and the simplified lignin model is a sugar. Sugars can also be considered a type of alcohol, but the bonds that form this alcohol are slightly different than the ones in the lignin model.

The mediators from Example 1 undergo electron transfer at low voltages and can transfer two electrons and a proton from a target molecule, so we thought those mediators might be perfect for this reaction too! Looking through some articles published in scientific journals saved us from wasting our time conducting these reactions in the lab. Other researchers had already demonstrated that those mediators will affect both the lignin and the part of wood used for paper.

Instead, the literature indicated that we should look at a proton-coupled electron-transfer mediator that transfers only one electron and one proton. As expected, we found that this mediator also undergoes direct electron transfer at a much lower potential than the direct electrochemical removal of electrons from either of the models. We've successfully exchanged the sledgehammer for the smaller hammer!

We then evaluated the ability of the mediator to remove one electron and one proton from the lignin model molecule. Since two electrons (yellow balls) and two protons (gray balls) must be removed from the alcohol to generate the product (green square), two mediator molecules (blue diamond) are required to transform one model alcohol (red square) to product as shown in Figure 1.2. The indirect electrochemical reaction of the mediator with the lignin model alcohol generated product. No product was formed in the indirection electrochemical reaction of the mediator with the sugar model and all the sugar model was recovered at the end of the reaction. Therefore, the mediator does not transfer a hydrogen atom (one electron and one proton) as shown in Figure 1.2.

Figure 1.2. The indirect electrochemical reaction of lignin and sugar model molecules



Encouraged by the reaction of the mediator with the lignin model, and lack of reaction with the sugar, we decided it was time to try the indirect electrochemical reaction with actual wood. The complicated analysis of the reaction products indicated that many of the alcohols in lignin linkages had been converted to the protected form, and no changes were detected in the part of the wood used for paper! **Despite the immense chemical complexity of wood, mediators enabled the transformation of just one part of the many complex molecules in wood**.

Scientists around the world are becoming increasingly interested in the ability of indirect electrochemistry to make new molecules or make known molecules in more efficient or environmentally friendly ways. Although the chemical reactions described in examples 1 and 2 will likely never be used directly in the commercial production of drug molecules or valuable chemicals from wood, future researchers may be able to improve upon these strategies to enable commercial applications. To further that goal, I've helped develop indirect electrochemistry lab experiments for undergraduate students, graduate students, and industrial scientists. These educational labs will be used for many years at multiple institutions and companies to provide other researchers with the knowledge and skills to develop their own new electrochemical reactions.