Meta-Mechanisms:

"Proving" in Organic Chemistry

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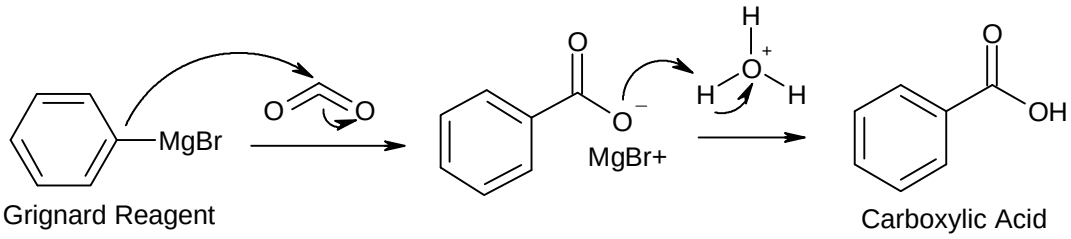
Organic chemistry is a division of chemistry concerned with carbon-containing compounds. An extremely diverse and complicated discipline, organic chemistry has substantial implications in technological, biological, and medicinal fields. This wide applicability owes itself to the exceptional bonding nature of carbon. Carbon can bond with itself and other atoms to an extent not possible with many other elements (Morrison 2). As a result, over a million compounds of carbons are known of today and thousands more are made each year. It is understandable then that one of the major areas of study within this discipline deals with how molecules react to form other compounds, how the atoms are arranged within those molecules, and what principles govern these reactions (49).

Chemists often approach these questions by developing a reaction mechanism. In short, reaction mechanisms describe in a step by step fashion what occurs on the molecular level as a reactant (starting material) is transformed into a product (Morrison 49). The following mechanism for the formation of a carboxylic acid from a Grignard reagent and carbon dioxide illustrates this idea.



These mechanisms describe molecular occurrences, such as the transfer of electrons as indicated by the curved arrows. One might wonder how the chemist decides if a particular mechanism is correct if he cannot directly observe it happening. Unexpectedly, the geometric notion of proof is applicable to this inquiry by allowing chemists to formulate a pseudo-axiomatic method for the establishment or “proving” of organic reaction mechanisms.

The geometric notion of proof is well within the comfort level of most people. A proof, as currently taught in high school and college geometry classes, is a list of statements and their justifications that leads from a hypothesis to a conclusion. A proof uses certain axioms, or assertions needing no proof, and logic to construct an argument that shows that a statement is necessarily true (Wikipedia). The resulting truth is a theorem that can be further employed to prove other statements. Subsequent use of theorems and axioms for proof has the effect of building comprehensive axiomatic systems like Euclidean geometry. The foundation of Euclidean geometry hinges upon the idea of deductive logic.

The deductive method is characterized by its general to specific approach to proofs. Using this method, one starts by devising a theory addressing a particular area of interest. From there, this theory is narrowed down into a testable hypothesis. Observations concerning this hypothesis are then collected and used for testing. The results of these tests function to confirm or refute the original theory (Trochim). In short, the deductive method is controlled by logic; if a statement follows logically from the axioms of a system the statement must be true (Stanbrough). This method works surprising well for mathematics based endeavors, but can these same constraints be applied to science, specifically to the empirical study of organic chemistry?

Nature, the focus of most scientific endeavors, has no rulebook. To use the deductive method in this respect, researchers would have to start with simple truths about nature and from them deduce other certainties. But, as nature has no set rules with which a researcher might begin his studies, the application of the deductive method to science presents problems. In response to this, science developed its own method: the inductive scientific method. The inductive method reverses the process of its antithesis and starts by drawing out observations from nature. These observations are then collated to find patterns that allow the development of

tentative hypotheses describing nature. Once these hypotheses are supported by enough observational data they are accepted as fact, theory, or law (Trochim). Thus, in the inductive method, observation rather than logic is paramount. If, in this method, an idea conflicts with observation, it is the idea, not the data, that needs to be changed (Stanbrough).

Chemistry, being an empirical science, is best studied using the latter of these two methods. However, when trying to prove reaction mechanisms, the inductive method still presents the researcher with difficulties. Within an empirical science, nothing, including reaction mechanisms, can ever be determined with one hundred percent accuracy; there is always some seed of doubt (Carpenter 1). How, then, does the chemist actually know what is going on at the molecular level in the reaction? While absolute certainty is an impossible goal, a chemist will seek the next closest thing. The chemist attempts to develop the best possible approach in order to have the greatest confidence in hypothesis induced from experimentation. In this endeavor, chemists flirt with certainty, and thus, despite the empirical and inductive nature of organic chemistry, the development of reaction mechanisms has its pseudo-axiomatic moments.

According to Carpenter, the best procedure devised so far for achieving this state of greatest confidence is as follows:

1. Formulate a hypothesis to fit the known facts.
2. Design and execute an experiment to test the hypothesis.
3. If the experimental results are consistent with the hypothesis (within the limits of experimental error) go to step 4, otherwise go to step 1.
4. If ‘all’ of the testable features of the hypothesis have been subjected to experimental scrutiny then stop, otherwise go to step 2 (2).

On first reading, this procedure may seem entirely viable and perhaps even a little obvious. One soon realizes, especially if attempting to perform this procedure, that this method is indefinite in length. The word ‘all’ in step four is misleading. It is impossible to experimentally test *all* the predictions suggested by a hypothesis as there are infinitely many possible and no research team

could ever expect to think of them all. Discouragingly, if a testable prediction is missed the omitted data could present a fatal flaw in research and destroy any theory that may be developed from that experiment in the future. Step four, therefore, should more accurately read: 'Return to step 2 indefinitely, or, stop if you've lost interest, run out of grant money, or gathered enough information for the purposes of your research'. Since the first part of the revised step 4 is not realistic and probably not what most chemists find joy in attempting, a chemist must get the most out of the time that is spent in this phase.

As laid out by Carpenter's procedure, the best possible approach to "proving" a reaction mechanism begins with developing the best possible hypothesis. Seeing as there are no specific guidelines for the formulation of such a hypothesis, this process is, in practice, somewhat 'hit or miss' in nature. Nonetheless it is important to keep some minimum standards in mind. A tentative hypothesis should be consistent with all available data, or at least, neutral to the data. A hypothesis in obvious conflict with data should be rethought and/or eliminated unless there exists compelling and independent evidence that the data addressed by the hypothesis are faulty. The predictions made from these tentative hypotheses should be as easily proven wrong as proven right. Furthermore, the logical principle of Occam's razor should always be kept in consideration. Occam's razor states that "one should not increase, beyond what is necessary, the number of entities required to explain something" (Heylighen) or, in other words, that hypotheses should be as simple as possible. A simple hypothesis helps the researcher avoid unnecessary variables or concepts that might introduce inconsistencies, ambiguities, or redundancy into the experiment. Lastly, as previously mentioned, when working within an inductive system, it is the hypothesis that must be changed to fit the data. It is also important to avoid hypothetical additions made solely for the purpose of explaining away inconsistencies or

conflicts in the data (Carpenter 3). Proposed reaction mechanisms also should not violate the laws of the physical sciences (i.e. thermodynamics, conservation of mass and energy, symmetry, etc.). While such laws are unproved hypotheses themselves, they are so widely accepted that they effectively occupy semi-axiomatic positions in this inductive system. A proposed mechanism challenging one of these laws would need an excessive amount of evidence to be accepted.

Once a hypothetical mechanism has been proposed it must be tested. This step opens up an entirely new can of worms. At this point researchers must ask themselves: What test should be performed? Like in the development of the hypothesis, there is also no established plan of action for this step. Researchers well versed in mechanistic determination all suggest different paths. Perhaps the most useful suggestion given is that anything is basically fair game. Lewis writes to this effect: “If you don’t know what to do next, do something” (478). Through this method, it is very likely to serendipitously uncover clues that may guide further testing. Beyond doing just about anything, chemists find it helpful to consider various questions concerning a broad range of chemical properties of the reaction. These questions serve to direct further study in a more purposeful manner. This sense of purpose should also be extended to the expected result of the reaction. To be useful, tests must give unambiguous results. If a test opens up an totally new mechanism controlling the reaction in question, the result is ambiguous and cannot be used to explain the unknown.

Inherently, there is an additional danger to bear in mind. Chemists must be vigilant not to transform their hypothesis into a pet theory. If one particular theory is favored exclusively it is easy to adapt the range of experimentation so that only those tests known to support the pet theory are considered. Theories should be readily dismissible and replaceable; emotional

attachment should be avoided. This vice affects even the greatest of researchers. Lewis recalls in his text a colloquium speaker making the following remark: "We've written this mechanism down so many times we're sure it's right" (479).

In fact, Lewis goes on to say that to prevent such pet theories, researchers should let their imagination run freely. Every theory, including those deemed absurd, should be considered. An absurd mechanism should be dismissed only on the basis of its incompatibility with the data and not on the fact that it is discordant with the prevailing theory of the day. He remarks: "Molecules are insensitive to scientific fashion and may behave in ways contrary to the current vogue. Many unheard-of mechanisms have been discovered in recent years; perhaps the next is lurking in your reaction" (479). While including the absurd, the researcher should also welcome the strange. Mechanisms that appear too normal do not inspire creativity in chemists. Normality is a dead end; it doesn't point specifically to any mechanistic developments. Sherlock Holmes, like any excellent mechanistic detective, realized this:

> It is a mistake to confound strangeness with mystery. The most commonplace crime is often the most mysterious, because it presents no new or special feature from which deductions may be drawn. This murder would have been infinitely more difficult to unravel had the body of the victim been simply found lying in the roadway without any of those outré and sensational accompaniments which have rendered it remarkable. These strange details, far from making the case more difficult, have really had the effect of making it less so (480).

Thus, as Holmes purports, uniqueness allows for the elimination of other hypotheses. It is not something for the researcher to shy away from.

Once the hypotheses are developed and the tests performed, the data can be analyzed in consideration of the individual hypotheses. Gradually, a researcher is able to rule out some of the proposed hypotheses. Much of this process is based on experience, intuition, and serendipity. If lucky, a family of hypotheses may all be eliminated except for one. This survivor is then

considered to be “established”, or a theory. This establishment does not mean, however, that the particular mechanism is correct: it is simply the most correct mechanism encountered thus far. The researchers have not, by any stretch of the imagination, conceived of all possible mechanisms so it is very possible that the actual mechanism has yet to occur to the researchers (Lewis 477). The inductive nature of chemistry allows for the adoption of this theory as fact, at least, until a better explanation surfaces. Theories can then be used like the theorems of deductive systems to offer support in the establishment of other theories.

The actual tests that are employed to distinguish between two proposed reactions can, in practice, be very complicated. While it is not necessary or feasible to expound on all these methods, the method of isotopic labeling is of particular importance in this mechanistic endeavor. A simple example of the great utility of labeling studies can be seen in this adaptation from Scharrer comparing two competing mechanisms for esterification or the process by which a carboxylic acid is converted into an ester. In this example, as in the previous example, the curved arrows represent the transfer of a pair of electrons.

Figure 1. Observed Reaction with Labeling.

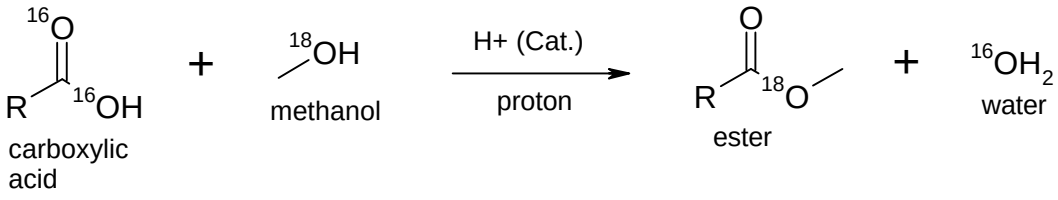


Figure 2. Proposed Reaction Mechanism #1.

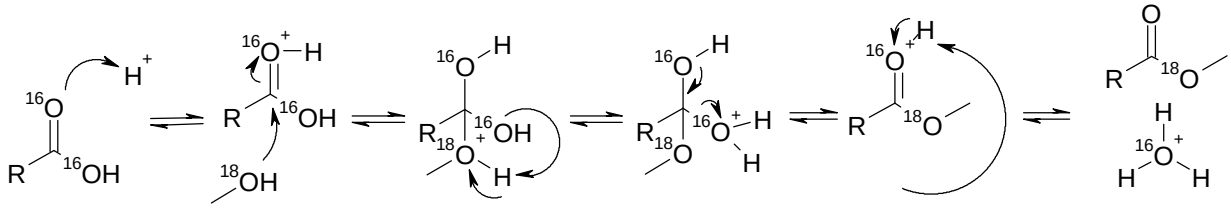
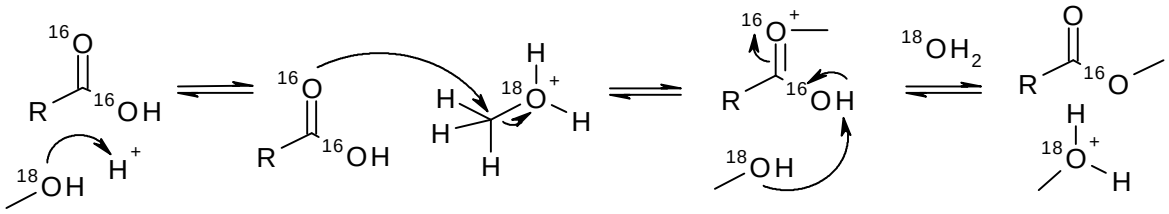


Figure 3. Proposed Reaction Mechanism #2.



This example of isotopic labeling in an esterification reaction uses oxygen-18, a radioactive isotope of the common and more stable oxygen-16, as a marker so that the oxygen of methanol molecule may be tracked through reaction. As seen in Figure 1, observations of the starting and ending materials point to the incorporation of the oxygen-18 into the ester. Figures 2 and 3 propose two possible ways that this reaction could proceed: by attack at the carbonyl or by deprotonation. The mechanism of Figure 2 illustrates the attack of oxygen-18 electrons of methanol at the carbonyl group (carbon double bonded to oxygen) of the carboxylic acid. This step is the defining characteristic of this mechanism. It directly leads to the incorporation of the oxygen-18 in the ester product. Figure 3 shows a mechanism whose defining characteristic is the deprotonation (or the removal of a hydrogen atom) of the protonated methanol ($CH_3OH_2^+$; positively charged product, as indicated by plus sign) by the carbonyl oxygen of the carboxylic acid. This step directly causes the incorporation of the oxygen-18 marker into the protonated methanol product. Thus, of the two proposed mechanisms, number one appears to best support the observed data. Number one is consistent with the labeling study (Figure 1), whereas in mechanism two the oxygen-18 marker is not incorporated into the ester products. With this evidence, mechanism two can be comfortably eliminated as a possibility. Conceivably, since all but one of the mechanisms have been eliminated in this example, the remaining mechanism one, is considered the “generally accepted” mechanism.

By “proving” this reaction occurs by mechanism number one, the chemist has gained innumerable tools. A “generally accepted” mechanism “make[s] up the framework upon which we hang the facts we learn” (Morrison 49). More specifically, this framework allows for the finding of patterns among a plethora of organic reactions. The recognition of patterns allows the chemist to locate apparently unrelated reactions and classify them as proceeding by identical or similar mechanisms without having to embark on the experimental process a second time. The establishment of one mechanism gives rise to the easy establishment of a multitude of other reactions; thus, the return on the investment of time into this research is immense and fruitful. In addition, knowing the pathway by which a reaction is thought to proceed allows the chemist to make logical and purposeful changes in reaction conditions and/or procedures in order to accelerate the reaction, increase the product yield, or obtain a different product altogether. The chemist no longer is subject to the confines of trial and error and therefore can exercise greater power over his field.

This overview of “proof” in organic reaction mechanisms made use of one axiom. It is axiomatic in this system that one cannot define a reaction mechanism with certainty and thus must reject that which is incompatible with experimental evidence. This axiom directs our treatment of “proof” into an inductive reasoning method by requiring evidence-backed hypotheses. Additionally, there are numerous pseudo-axioms that govern the choice of hypotheses. The laws of the physical science are included among these. These pseudo-axioms permit the justification of hypotheses by attesting to their feasibility in nature. Most importantly though, these axioms aid in the development of a testable hypothesis and provide for the formulation of theories. The theories, like the theorems of geometry, are useful for future research and development of mechanisms. In this regard, organic chemistry draws deeply upon

the idea of geometric proof for the construction of a viable system under which research is conducted with some sense of larger purpose and applicability. Without such a system, experimentation in chemistry and perhaps all laboratory sciences would cease to have meaning.

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