DETERMINATION OF MECHANISMS

The determination of the mechanism of a chemical reaction is much more than an intellectual exercise. Unravelling the proposed steps by which the reagents in a reaction mixture are converted to the observed products takes careful and conservative interpretation of painstaking experiments. The mechanism is a theory, and, like all theories in science, is not static: it becomes more detailed, or changes completely, as new experiments are applied to the problem. This theory of how a reaction occurs makes possible an understanding of why it does and thus: prediction of conditions which will assist or hinder the reaction, manipulation of stereochemistry, and prediction of totally new reactions. In addition, the understanding of how and why a reaction occurs provides a framework to aid recall of the outcome of specific reactions.

In the introductory courses Organic Chemistry I and II, mechanistic theories will be used extensively to help foster understanding of what reactions occur and why. For selected reactions, the experimental basis for the conclusions and the reasoning by which the conclusions were reached will also be discussed. These experimental details provide a glimpse into the core scientific basis of organic chemistry and are thus *very important*.

The most common information used to determine reaction mechanisms is outlined below. An ancient principle is applied to the study of mechanisms, and in most other areas of science: Occam's Razor. Occam's (Ockham's) Razor (Principle) is that the simplest explanation is most likely to be correct; the concept precedes modern science by many years but is actually demonstrable with modern statistics.

1. IDENTIFICATION OF STARTING MATERIAL AND PRODUCTS

Methods

Separation of products of the reaction by distillation, crystallization and chromatography is followed by identification using chemical tests, infrared, mass (MS) and NMR spectroscopy. Starting materials must be tested for purity. Additional starting materials are often designed and synthesized to test various aspects of the mechanism, the reaction repeated and the products determined. Often trace amounts of surprising products provide key information.

Interpretation

The proposed mechanism must explain : all of the products, without excessive elaborations and exceptions; the dependence of the reaction products on starting material structure (substrate, nucleophile or electrophile); any observed regioselectivity. Often little information is gained about how the reaction occurred by looking at the products, so additional experiments are necessary.

2. KINETICS / RATE LAW

Methods

A series of reactions must be performed to determine the rate law. The rate must be determined for 10-20 concentrations of each reagent; each of these measurements requires measuring the concentration of one or more products or reagents as a function of time (about 20 measurements). Determination of the rate law thus requires hundreds of concentration measurements for each compound. Alternate substrates should also be tested to ensure that they follow the same rate law. The presence or absence of equilibria between reagents and products should be tested by addition of products or product analogues.

Interpretation

The rate law reveals the chemical species which are included in the transition state (activated complex), i.e. the rate-limiting step. The mechanism proposed must explain the rate law under all conditions. It must explain the direction (and size) of the rate change with structure of the organic and inorganic reagents. If intermediate compounds are proposed, they

must react at least as fast as the original reagent.

3. CATALYSIS

Methods

Reaction rates and rate laws must be determined to ensure that the suspect catalyst does indeed affect the rate and the products must be examined to ensure that it has not been consumed (sometimes catalyst is casually applied to reagents which are changed but not incorporated into the products).

Interpretation

The proposed mechanism must incorporate catalytic information in a chemically reasonable manner. For example, the mechanism for an acid-catalyzed reaction should involve proton transfers, not bases. Inhibition (negative catalysis) must also be explained.

4. STEREOCHEMISTRY

Method

Enantiomerically pure reagents must be obtained, either by synthesis from natural products or by resolution of racemic materials. Product stereochemistry can be determined by comparison of optical rotation with known materials, or by taking the NMR spectrum in a chiral medium; since the enantiomers behave as if they were diastereomers in a chiral solution, their spectra are different (the ability to see the difference is tested with the racemate).

Interpretation

Stereospecific reactions must preserve old bonds while new ones are being formed. The mechanism must explain the existence and the direction of any stereospecificity, stereoselectivity or racemization.

5. SOLVENT EFFECT

The solvent can affect both the identity of the products (e.g., by incorporation) and the rate of the reaction. The involvement of the solvent in the reaction is often difficult to unravel because its concentration is essentially unchanged during the reaction. The mechanism must explain the effect on reaction rate of different solvents and any incorporation of solvent into the reaction products.

6. ISOTOPES

Careful synthesis of model starting materials with unnatural isotopes is often difficult. Determination of the location of an isotope is usually done by NMR or MS, and does not require radioactivity. Most commonly, isotopes are used as tracers, to determine the route that a particular atom takes during the reaction (e.g., in a rearrangement). In addition, isotopes (because of different masses) react at slightly different rates; if the bond to the isotope is formed or broken in the rate-limiting step, the rate will be affected by isotopic substitution, the "kinetic isotope effect". The mechanism must explain both the location and the effect on rate.

7. OTHER REACTION CHARACTERISTICS

Occasionally strange behavior is observed, such as a reaction rate or outcome depending on the size or material of the container, as it often does for free radical chain reactions. Sometimes there are hidden reagents or catalysts like water and oxygen, which divert reactions (check the products!), especially those involving organometallic compounds.

SUGGESTED READINGS

O.T. Benfey, *Introduction to Organic Reaction Mechanisms*, McGraw-Hill, NY 1970
A.A. Frost and R.G. Pearson, *Kinetics and Mechanism*, 2nd Ed., Wiley, NY 1961
E.S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt Reinhart Winston, NY 1959.