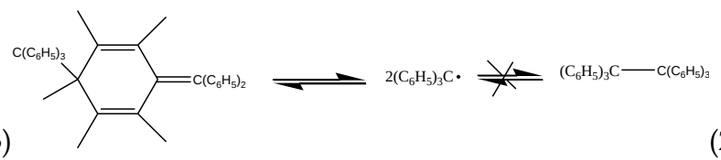
Investigation of reaction mechanism

The mechanism of a chemical reaction can never be proven to be correct. However sufficient data can be accumulated by using different methods to show that one or more theoretically possible mechanisms are just compatible with experimental results. Different methods used to determine the reaction mechanism are discussed below:

1) **Nature of the products.**

Perhaps the most important information about the mechanism of that reaction can be gathered by establishing the structure of the products and then relating this to the structure of the reactants. If two or more products are formed then their relative proportion also gives us important information.

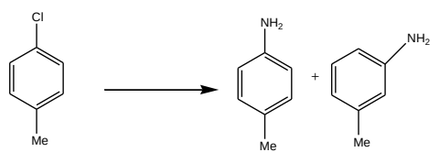
It is very important to determine the correct structure of the products; otherwise the wrong information creates confusion. For example **yellow triphenylmethyl radical** , obtained from the action of silver on triphenylmethyl chloride in 1900, readily forms a colourless dimer (m.w. = 486) which was reasonably assumed to be hexaphenylethane (2) with thirty 'aromatic' hydrogen atoms. Only after nearly seventy years (in 1968) did the n.m.r. spectrum of the dimer (with only twenty-five aromatic' (H), four 'dienic' (H), and one 'saturated' (H), hydrogen atoms) demonstrate that it could not have the hexaphenylethane structure (2) and was, in fact (3):



(3) (2)

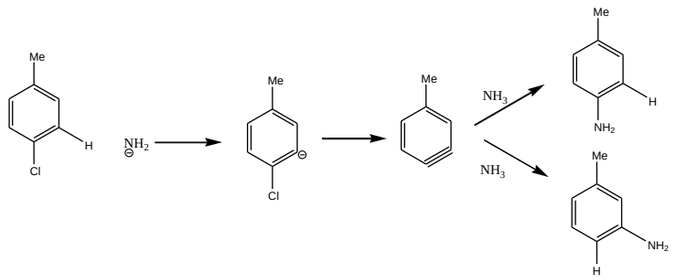
With this point numerous small details of the behaviour of (3) and of its dimer, that had previously appeared anomalous, became understandable.

Information about the products of a reaction can be particularly informative **when one of them is quite unexpected**. Thus the reaction of chloro-4-methylbenzene (p-chlorotoluene, 4) with amide ion, $^{-}NH_2$ in liquid ammonia is found to lead not only to the expected 4-methylphenylamine (p-toluidine, 5), but also to the quite unexpected 3-methylphenylamine (m-toluidine, 6), which is in fact the major product.



Expected Unexpected

The latter clearly cannot be obtained from (4) by a simple substitution process, and either must be formed from (4) via a different pathway than (5), or if the two products are formed through some common intermediate then clearly (6) cannot be formed by a direct substitution either.



2) Kinetic Data

Still the kinetic data provides us the largest body of information about reaction pathways, but it requires a deep look for the interpretation of kinetic data, as it is not always as simple as it looks at first sight. Many times the effective reacting species, whose concentration actually determines the reaction rate, differ from the starting materials of the reaction.

For example in **aromatic nitration** the effective attacking species is usually $^{+}N0_2$, but it is HN03 that we put into the reaction mixture, and whose changing concentration we are measuring; the relationship between the two may be complex and so, therefore, may be the relation between the rate of reaction and [$HN0_3$]. Despite the fact that the essential reaction is a simple one, it may not be easy to deduce this from the quantities that we can readily measure.

Second example is the **hydrolysis of the alkyl halide,** RHal, in aqueous solution, which is found to follow the rate equation as given below:

$$\text{Rate} = k_1[\text{RHal}]$$

it is not safe to conclude that the rate-determining step does not involve the participation of water, simply due to the reason that [H_20] does not appear in the rate equation. Actually water is used as the solvent in this reaction and its concentration remains unchanged whether or not it actually participated in the rate-limiting stage. This thing can be checked by carrying out the hydrolysis in another solvent, e.g. HCO_2H, and by using a much smaller concentration of water as a potential nucleophile. The hydrolysis may then be found to follow the rate equation,

$$\text{Rate} = K_2[\text{RHal}][H_2O]$$

but the actual mechanism of hydrolysis could well have changed on altering the solvent, so we are not, in a position to tell about what actually went on in the original aqueous solution.

For the organic reactions that are carried out in solution, quite small changes in the solvent can affect the reaction rates and mechanisms. Particularly those reactions in which polar intermediates, for example carbocations or carbanions are involved, solvent molecules made an envelope around them which greatly affects their stability (and their ease of formation although it is strongly influenced by the composition and nature of the solvent employed, particularly its polarity and ion-solvating capabilities.

By contrast, reactions that involve radicals are much less influenced by the nature of the solvent (unless this is itself capable of reacting with radicals), but are greatly influenced by the addition of radical sources (e.g. peroxides) or radical absorbers (e.g. quinones), or

by light which may initiate reaction through the production of radicals by photochemical activation,

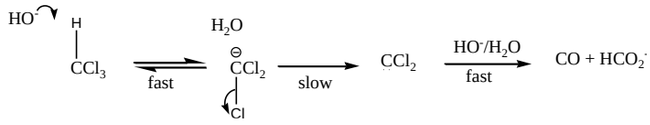
e.g. Br2 ---------- Br· ·Br.

A reaction that is found, on kinetic investigation, to proceed unexpectedly faster or slower than the apparently similar reactions, under comparable conditions, of compounds of related structure suggests that it probably follows different, or modified, pathway from the general one that might otherwise have been assumed for the series.

Thus the observed rates of hydrolysis of the chloromethanes with strong bases are found, under comparable conditions, to vary as follows,

CH3CI » CH2 Cl2 « CHCI3 » CCI4

clearly suggesting that trichloromethane undergoes hydrolysis in a different manner from the other compounds (cf. p. 267).



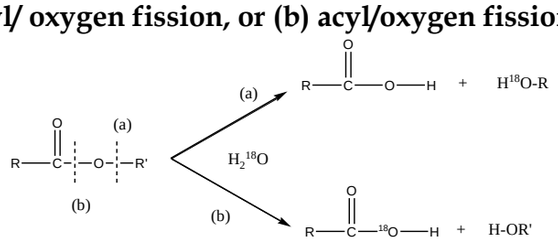
3) The use of isotopes

During the mechanism investigation, an important question is whether a specific bond is broken in a rate determining step or not. For example if we want to know about a C-H bond, we have to compare its rate of reaction with C-D, in which H is replaced with its isotope D. Both bonds are chemically of same nature, but replacing H with D will change their bond strength as the masses are different. This ultimately will change the rate of breaking the bond under same reaction conditions, as greater masses makes bond stronger.

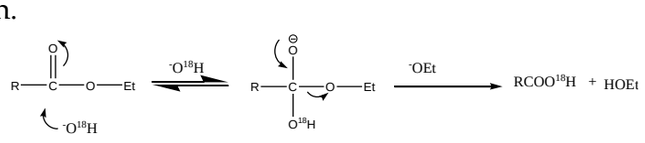
The weaker C—H bond being broken more rapidly than the stronger C—D bond.

For example it is found that Ph $_2$CHOH is oxidized 6-7 times as rapidly as Ph $_2$CDOH, the reaction is said to exhibit a **primary kinetic isotope** effect and breaking of the C-H bond must clearly be involved in the rate limiting step of the reaction. By contrast **benzene, C_6H_6 , and hexadeuterobenzene, C_6D_6 , are found to undergo nitration at essentially , the same rate**, and C-H bond-breaking, that must occur at some stage in the overall process, thus cannot be involved in the rate limiting step.

Isotopes can also be used to solve mechanistic problems that are non-kinetic. **Thus the aqueous hydrolysis of esters to yield an acid and an alcohol could, in theory, proceed by cleavage at (a) alkyl/ oxygen fission, or (b) acyl/oxygen fission.**

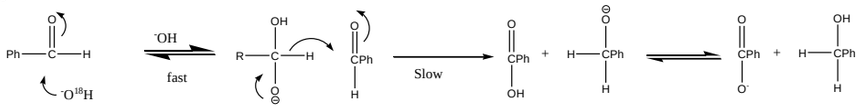


If the reaction is carried out in water enriched in the heavier oxygen isotope ^{18}O, (a) will lead to an alcohol which is ^{18}O enriched and an acid which is not, while (b) will lead to an O^{18} enriched acid but a normal alcohol. **Most simple esters are in fact found to yield an ^{18}O enriched acid** indicating that hydrolysis, under these conditions, proceeds via (b) acyl/oxygen fission.



It should be noted that these results are only valid provided that neither acid nor alcohol, once formed, can itself exchange its oxygen with water enriched in ^{18}O, as has indeed been shown to be the case.

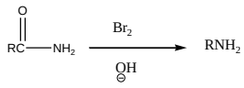
Heavy water, D_2O, has often been used in a rather similar way. **Thus in the Cannizzaro reaction of benzaldehyde the question arises of whether the second hydrogen atom that becomes attached to carbon, in the molecule of phenylmethanol (benzyl alcohol) that is formed, comes from the solvent (H_2O) or from a second molecule of benzaldehyde.**



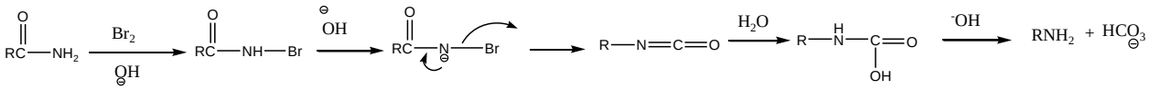
Carrying out the reaction in D_2O is lead to the information **that no PhCHDOH is formed** thus demonstrating that second hydrogen atom could not have come from water, and must be transformed from 2nd molecule of benzaldehyde.

4) The study of intermediates

I) Among the most concrete evidences obtainable about the mechanism of a reaction is that provided by the actual isolation of one or more intermediates from the reaction mixture. Thus in the Hofmann reaction by which amides

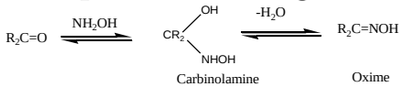


are converted into amines, it is, with care, possible to isolate the N-bromoamide, RCONHBr, its anion, $RCONBr^-$, and an isocyanate, RNCO; thus going some considerable way to elucidate the overall mechanism of the reaction.



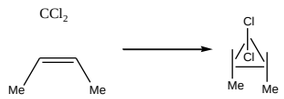
It is of course necessary to confirm that any species isolated really is an intermediate—and not merely an alternative product. **An intermediate is specie that, under the normal reaction conditions, can be converted into the usual reaction products at a rate not less than the overall reaction under the same conditions.**

II) It is more common that no intermediate can be isolated. However it does not mean that intermediate is not formed at all, but it may be possible that we are unable to isolate it. In these conditions spectroscopic measurements are used to identify any intermediate if formed. **Thus in the formation of oximes from a number of carbonyl compounds by reaction with hydroxylamine, the infra-red absorption band characteristic of C=O in the starting material disappears rapidly, and may have gone completely before the band characteristic of C=N in the product even begins to appear.**



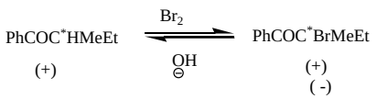
Clearly an intermediate must be formed, and further evidence suggests that it is the carbinolamine, which forms rapidly and then breaks down only slowly to yield the products, the oxime and water.

III) There are certain reactions in which we have certain reasons to believe that an intermediate is involved. The possibility of formation of these intermediates can be checked by addition of a reactive specie that will react with the supposed intermediate and form a product that otherwise was impossible. **Thus the intermediate can be trapped and can be isolated from the reaction.** Thus in the **hydrolysis of trichloromethane** with strong bases, the highly electron-deficient dichlorocarbene, CCl_2 , which has been suggested as a labile intermediate, was 'trapped' by introducing into the reaction mixture the electron-rich species cis but-2-ene, and then isolating the resultant stable cyclopropane derivative whose formation can hardly be accounted for in any other way.

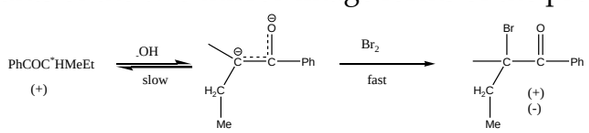


5) Stereochemical criteria

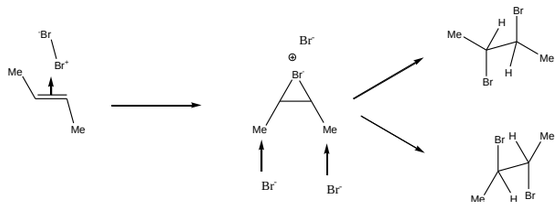
Information about the stereochemical course followed by a particular reaction can also provide useful insight into its mechanism. Thus the fact that the base-catalysed bromination of an optically active stereoisomer of the ketone



leads to an optically inactive racemic product, indicates that the reaction must proceed through a planar intermediate, which can undergo attack equally well from either side leading to equal amounts of the two mirror-image forms of the product.



Then again, the fact that cyclopentene adds on bromine under polar conditions to yield the trans dibromide only, indicates that the mechanism of the reaction cannot simply be direct, one-step addition of the bromine molecule to the double bond, for this must lead to the cis dibromide :



The addition must be at least a two-step process. Reactions like this, which proceed so as to give largely—or even wholly—one stereoisomer out of the two alternative possible, are said to be stereo selective.

Stereoselectivity:

In chemistry, **stereoselectivity**[1] is the property of a chemical reaction in which a single reactant forms an unequal mixture of stereoisomers during a non-stereospecific creation of a new stereocenter or during a non-stereospecific transformation of a pre-existing one.[2] The selectivity arises from differences in steric

effects and electronic effects in the mechanistic pathways leading to the different products. Stereoselectivity can vary in degree but it can never be total since the activation energy difference between the two pathways is finite. Both products are at least possible and merely differ in amount. However, in favorable cases, the minor stereoisomer may not be detectable by the analytic methods used.

An **enantioselective** reaction is one in which one enantiomer is formed in preference to the other, in a reaction that creates an optically active product from an achiral starting material, using either a chiral catalyst, an enzyme or a chiral reagent. The degree of selectivity is measured by the enantiomeric excess. An important variant is kinetic resolution, in which a pre-existing chiral center undergoes reaction with a chiral catalyst, an enzyme or a chiral reagent such that one enantiomer reacts faster than the other and leaves behind the less reactive enantiomer, or in which a pre-existing chiral center influences the reactivity of a reaction center elsewhere in the same molecule.

A **diastereoselective** reaction is one in which one diastereomer is formed in preference to another (or in which a subset of all possible diastereomers dominates the product mixture), establishing a preferred relative stereochemistry. In this case, either two or more chiral centers are formed at once such that one relative stereochemistry is favored,[3] or a pre-existing chiral center (which needs not be optically pure) biases the stereochemical outcome during the creation of another. The degree of relative selectivity is measured by the diastereomeric excess.

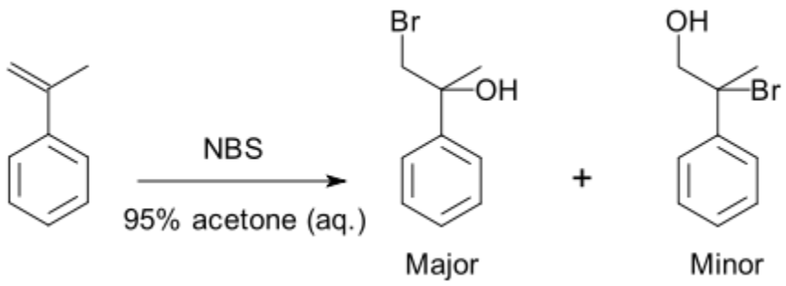
Stereoconvergence can be considered an opposite of stereospecificity, when the reaction of two different stereoisomers yield a single product stereoisomer.

Regioselectivity:

The reaction in which the bond making or breaking takes place preferentially to one direction is called a regioselective reaction.

regioselectivity is the preference of one direction of chemical bond making or breaking over all other possible directions.[1][2] It can often apply to which of many possible positions a reagent will affect, such as which proton a strong base will abstract from an organic molecule, or where on a substituted benzene ring a further substituent will add.

A specific example is a halohydrin formation reaction with 2-propenylbenzene:[3]



Because of the preference for the formation of one product over another, the reaction is selective. This reaction is regioselective because it selectively generates one constitutional isomer rather than the other.

Chemoselectivity is the preferential outcome of a chemical reaction over a set of possible alternative reactions.[1]

In another definition, chemoselectivity refers to the selective reactivity of one functional group in the presence of others; often this process in convoluted and protecting groups are on the molecular connectivity alone.[*clarification needed*] Such predictions based on connectivity are generally considered plausible, but the physical outcome of the actual reaction is ultimately dependent on a number of factors that are practically impossible to predict to any useful accuracy (solvent, atomic orbitals, etc.).

Chemoselectivity can be difficult to predict, but observing selective outcomes in cases where many reactions are plausible, is common. Examples include the selective organic reduction of the greater relative chemoselectivity of sodium borohydride reduction versus lithium aluminium hydride reduction. In another example, the compound 4-methoxyacetophenone is oxidized by bleach at the ketone group at high pH (forming the carboxylic acid) and oxidized by EAS (to the aryl chloride) at low pH.[2].