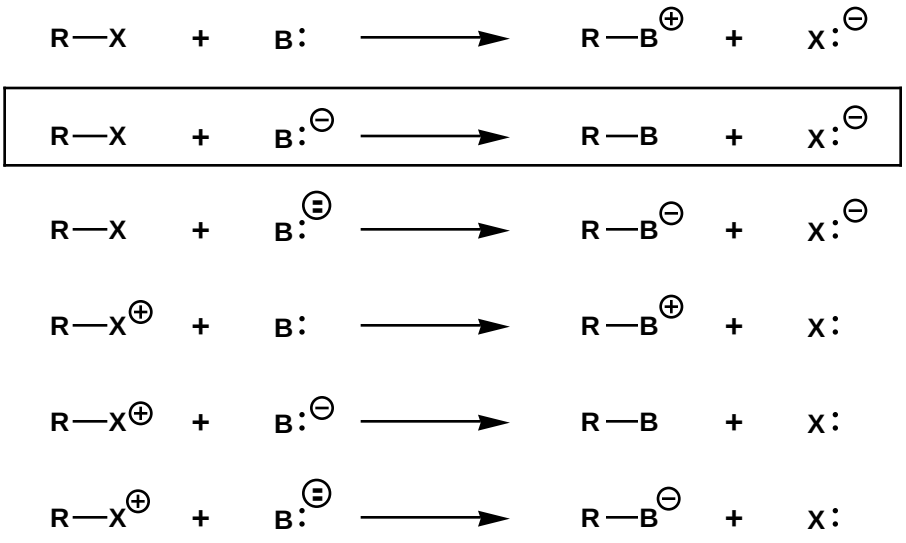
Text Related to Segment 13.01 ©2002 Claude E. Wintner

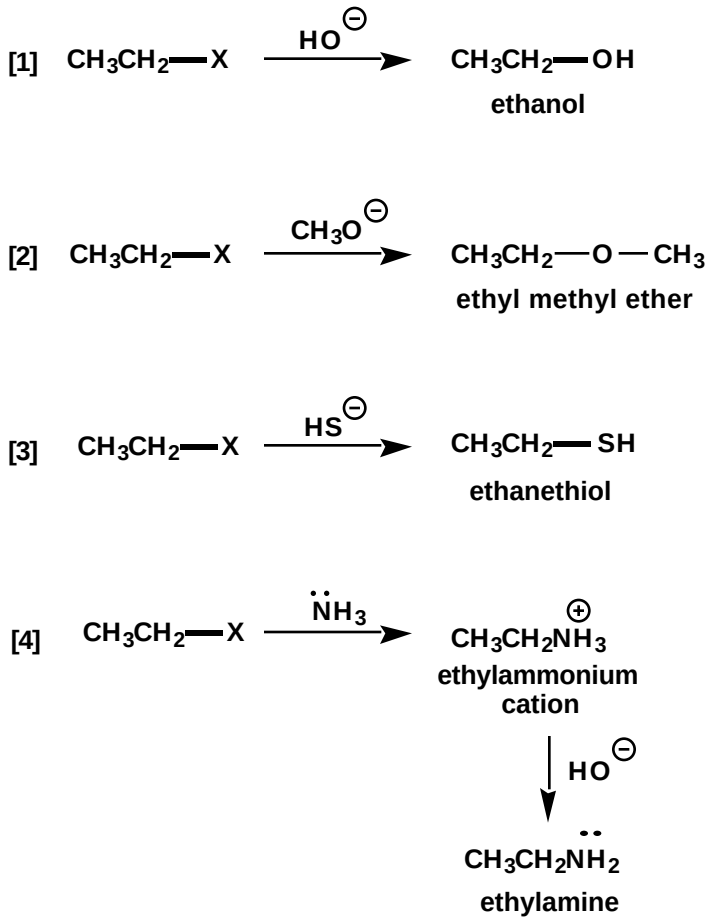
A large and common group of organic chemical transformations involves the substitution of one nucleophile, covalently bonded to tetrahedral carbon, by another nucleophile, which in turn forms a new covalent bond with the carbon atom. The leaving and entering nucleophiles, and also the substrates, may or may not carry charge. Several possible generalized cases are shown below, in our first figure, with a box highlighting one very common form:



various charge forms of substitution of one nucleophile by another

We are interested in using such reactions in synthesis and in understanding them when they are found to occur in metabolism or in other natural situations. To this end it is useful to know as much as possible about the mechanisms which govern the reactions, that is, to have a detailed molecular understanding of how they occur; for if we have grasped the mechanism of a reaction, then we will be in a far better position to employ the reaction effectively than if we have not. Thus, much of our ensuing discussion will be mechanistic.

The next figure lists a few nucleophilic substitution reactions involving commonly encountered functionalities with, in each instance, the ethyl moiety as the illustrating hydrocarbon group. Note, then, that these all are reactions occurring at a primary carbon atom. We soon shall see that this is an important point. Furthermore, as will be emphasized in the next segment, all of these reactions exhibit second-order kinetics.



examples of S_N2 reactions with ethyl halides

A central governing principle should be recognized: there is a general thermodynamic limitation, summed up by the statement that strong bases displace weak ones, while the reverse does not occur. Thus, in reaction [1] the competitors are hydroxide anion and halide anion; the former is stronger, and displaces the latter,

resulting in the synthesis of an alcohol, just as the reaction of hydroxide anion with hydrogen bromide leads to the formation of water. Reaction [2] resembles reaction [1], but the base, being an alcoholate (also called alkoxide) anion — in this case methylate (methoxide) anion — leads to the product ethyl methyl ether. We should keep in mind here what we already have learned during the course of our treatment of pK_A values: alkoxides are stronger bases than is hydroxide. Thus, a base stronger than hydroxide ion will be needed to remove the proton from methanol in order to produce the methoxide anion to initiate reaction [2], and, furthermore, the reaction cannot be carried out in the presence of water.

Reaction [3] is the sulfur analog of [1], leading to ethanethiol. In our discussion of nucleophilicity we already have alluded to the observation that, factors of solvent and concentration being equal, in protic solvents the rates of reactions which employ sulfur as the attacking atom generally are a great deal faster than the corresponding reactions that use oxygen nucleophiles. It also should be mentioned in these brief preliminary comments that polar aprotic (non-protic) solvents, which effectively decrease hydrogen bonding to nucleophiles and hence free them for reaction, quite generally enhance the rates of such reactions relative to the same reactions run in protic solvents.

Reaction [4] is an example of a substitution reaction initiated by the common electrically neutral nucleophile, ammonia. Note that since the nucleophile is electrically neutral, while the leaving group carries negative charge, the product remaining must bear positive charge, as it does. (This is the first general case of the first figure in this segment.) The resulting ethylammonium cation may be deprotonated at nitrogen by addition of base, to yield the electrically neutral ethylamine. The net result is to convert ammonia into a primary amine.