In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.

In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base.

In the next few sections, we are going to be discussing some general aspects of nucleophilic substitution reactions, and in doing so it will simplify things greatly if we can use some abbreviations and generalizations before we dive into real examples.

Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. In the same way, we will see later that nucleophiles and leaving groups are sometimes protonated and sometimes not, so for now, for the sake of simplicity, we will not include protons on 'Nu' or 'X'. We will generalize the three other groups bonded on the electrophilic central carbon as R\(_1\), R\(_2\), and R\(_3\): these symbols could represent hydrogens as well as alkyl groups. Finally, in order to keep figures from becoming too crowded, we will use in most cases the line structure convention in which the central, electrophilic carbon is not drawn out as a 'C'.

Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction:

The functional group of alkyl halides is a carbon-halogen bond, the common halogens being fluorine, chlorine, bromine and iodine. With the exception of iodine, these halogens have electronegativities significantly greater than carbon. Consequently, this functional group is polarized so that the carbon is electrophilic and the halogen is nucleophilic, as shown in the drawing on the right.

Two characteristics other than electronegativity also have an important influence on the chemical behavior of these compounds. The first of these is *covalent bond strength*. The strongest of the carbon-halogen covalent bonds is that to fluorine. Remarkably, this is the strongest common single bond to carbon, being roughly 30 kcal/mole stronger than a carbon-carbon bond and about 15 kcal/mole stronger than a carbon-hydrogen bond.
Because of this, alkyl fluorides and fluorocarbons in general are chemically and thermodynamically quite stable, and do not share any of the reactivity patterns shown by the other alkyl halides. The carbon-chlorine covalent bond is slightly weaker than a carbon-carbon bond, and the bonds to the other halogens are weaker still, the bond to iodine being about 33% weaker. The second factor to be considered is the relative stability of the corresponding halide anions, which is likely the form in which these electronegative atoms will be replaced. This stability may be estimated from the relative acidities of the H-X acids, assuming that the strongest acid releases the most stable conjugate base (halide anion). With the exception of HF ($pK_a = 3.2$), all the hydrohalic acids are very strong, small differences being in the direction $\text{HCl} < \text{HBr} < \text{HI}$.

In order to understand why some combinations of alkyl halides and nucleophiles give a substitution reaction, whereas other combinations give elimination, and still others give no observable reaction, we must investigate systematically the way in which changes in reaction variables perturb the course of the reaction. The following general equation summarizes the factors that will be important in such an investigation.

$$\text{R} - \text{X} + \text{Nu} \xrightarrow{\text{Solvent}} \text{Products}$$

One conclusion, relating the structure of the R-group to possible products, should be immediately obvious. If R has no beta-hydrogens an elimination reaction is not possible, unless a structural rearrangement occurs first. The first four halides shown on the left below do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds.

It is also worth noting that $sp^2$ hybridized C–X compounds, such as the three on the right, do not normally undergo nucleophilic substitution reactions, unless other functional groups perturb the double bond(s).

Using the general reaction shown above as our reference, we can identify the following variables and observables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Observables</th>
</tr>
</thead>
<tbody>
<tr>
<td>R change α-carbon from 1º to 2º to 3º if the α-carbon is a chiral center, set as (R) or (S)</td>
<td>Products substitution, elimination, no reaction. Stereospecificity if the α-carbon is a chiral</td>
</tr>
<tr>
<td>X change from Cl to Br to I (F is relatively unreactive)</td>
<td>Nu: change from anion to neutral; change basicity; change polarizability</td>
</tr>
<tr>
<td>Nu: change from anion to neutral; change basicity; change polarizability</td>
<td>Solvent polar vs. non-polar; protic vs. non-protic</td>
</tr>
<tr>
<td>Solvent polar vs. non-polar; protic vs. non-protic</td>
<td></td>
</tr>
</tbody>
</table>

[Diagram showing different alkyl halides and their reaction products]
When several reaction variables may be changed, it is important to isolate the effects of each during the course of study. In other words: only one variable should be changed at a time, the others being held as constant as possible. For example, we can examine the effect of changing the halogen substituent from Cl to Br to I, using ethyl as a common R–group, cyanide anion as a common nucleophile, and ethanol as a common solvent. We would find a common substitution product, $C_2H_5–CN$, in all cases, but the speed or rate of the reaction would increase in the order: Cl < Br < I.

This reactivity order reflects both the strength of the C–X bond, and the stability of $X^(-)$ as a leaving group, and leads to the general conclusion that alkyl iodides are the most reactive members of this functional class.