# Nucleophilic Substitution

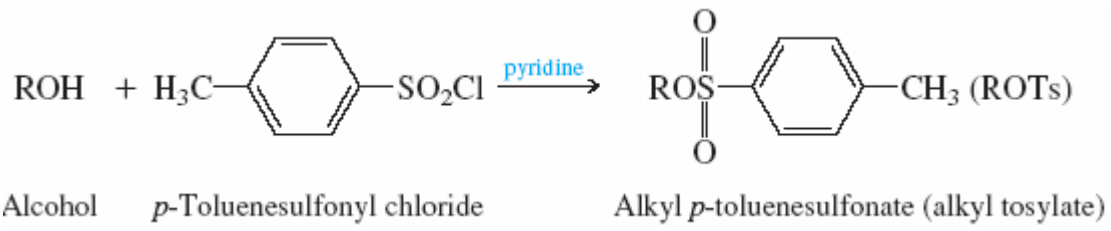
## SUMMARY

Section 8.1 Nucleophilic substitution is one of the main methods for functional group transformations. Examples of synthetically useful nucleophilic substitutions were given in Table 8.1. It is a good idea to return to that table and review its entries now that the details of nucleophilic substitution have been covered.

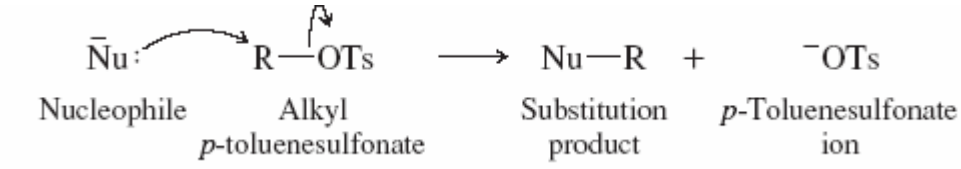
Sections 8.2–8.10 These sections show how a variety of experimental observations led to the proposal of the $S_N1$ and the $S_N2$ mechanisms for nucleophilic substitution. Summary Table 8.9 integrates the material in these sections.

Section 8.11 When nucleophilic substitution is used for synthesis, the competition between substitution and elimination must be favorable. However, *the normal reaction of a secondary alkyl halide with a base as strong or stronger than hydroxide is elimination (E2).* Substitution by the $S_N2$ mechanism predominates only when the base is weaker than hydroxide or the alkyl halide is primary. Elimination predominates when tertiary alkyl halides react with any anion.

Section 8.12 Nucleophilic substitution can occur with leaving groups other than halide. Alkyl *p*-toluenesulfonates (*tosylates*), which are prepared from alcohols by reaction with *p*-toulenesulfonyl chloride, are often used.

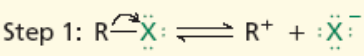
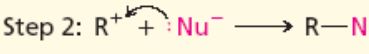
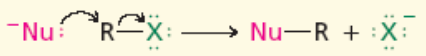
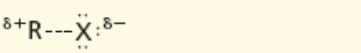
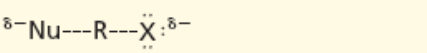



In its ability to act as a leaving group, *p*-toluenesulfonate is even more reactive than iodide.




Section 8.13 The reactions of alcohols with hydrogen halides to give alkyl halides (Chapter 4) are nucleophilic substitution reactions of alkyloxonium ions in which water is the leaving group. Primary alcohols react by an $S_N2$-like displacement of water from the alkyloxonium ion by halide. Secondary and tertiary alcohols give alkyloxonium ions which form carbocations in an $S_N1$-like process. Rearrangements are possible with secondary alcohols, and substitution takes place with predominant, but not complete, inversion of configuration.

**TABLE 8.9** Comparison of $S_N1$ and $S_N2$ Mechanisms of Nucleophilic Substitution in Alkyl Halides

| | $S_N1$ | $S_N2$ |
|---|---|---|
| **Characteristics of mechanism** | Two elementary steps:<br>Step 1:  <br>Step 2:  <br>Ionization of alkyl halide (step 1) is rate-determining. (Section 8.8) | Single step:<br>  <br>Nucleophile displaces leaving group; bonding to the incoming nucleophile accompanies cleavage of the bond to the leaving group. (Sections 8.3 and 8.5) |
| **Rate-determining transition state** |  <br>(Section 8.8) |  <br>(Sections 8.3 and 8.5) |
| **Molecularity** | Unimolecular (Section 8.8) | Bimolecular (Section 8.3) |
| **Kinetics and rate law** | First order:<br>Rate = $k$[alkyl halide]<br>(Section 8.8) | Second order:<br>Rate = $k$[alkyl halide][nucleophile]<br>(Section 8.3) |
| **Relative reactivity of halide leaving groups** | RI > RBr > RCl >> RF<br>(Section 8.2) | RI > RBr > RCl >> RF<br>(Section 8.2) |
| **Effect of structure on rate** | $R_3CX > R_2CHX > RCH_2X > CH_3X$<br>Rate is governed by stability of carbocation that is formed in ionization step. Tertiary alkyl halides can react only by the $S_N1$ mechanism; they never react by the $S_N2$ mechanism. (Section 8.9) | $CH_3X > RCH_2X > R_2CHX > R_3CX$<br>Rate is governed by steric effects (crowding in transition state). Methyl and primary alkyl halides can react only by the $S_N2$ mechanism; they never react by the $S_N1$ mechanism. (Section 8.6) |
| **Effect of nucleophile on rate** | Rate of substitution is independent of both concentration and nature of nucleophile. Nucleophile does not participate until after rate-determining step. (Section 8.8) | Rate depends on both nature of nucleophile and its concentration. (Sections 8.3 and 8.7) |
| **Effect of solvent on rate** | Rate increases with increasing polarity of solvent as measured by its dielectric constant $\epsilon$. (Section 8.12) | Polar aprotic solvents give fastest rates of substitution; solvation of $Nu:^-$ is minimal and nucleophilicity is greatest. (Section 8.12) |
| **Stereochemistry** | Not stereospecific: racemization accompanies inversion when leaving group is located at a chirality center. (Section 8.10) | Stereospecific: 100% inversion of configuration at reaction site. Nucleophile attacks carbon from side opposite bond to leaving group. (Section 8.4) |
| **Potential for rearrangements** | Carbocation intermediate capable of rearrangement. (Section 8.11) | No carbocation intermediate; no rearrangement. |