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# MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS,  
AND STRUCTURE

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SIXTH EDITION

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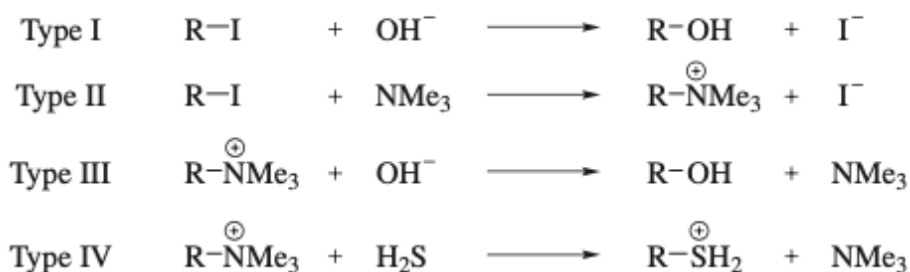
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# Aliphatic Substitution: Nucleophilic and Organometallic

In nucleophilic aliphatic substitution the attacking (electron donating) reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:



This equation says nothing about charges. Nucleophile Y may be neutral or negatively charged; RX may be neutral or positively charged; so there are four charge types, examples of which are



In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

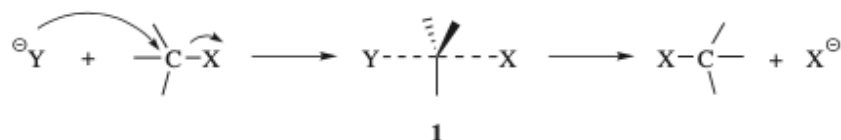
Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the above reaction between RI and NMe<sub>3</sub> is an *alkylation* of trimethylamine. Similarly, nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile.

## MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions. In all of them, however, the attacking reagent carries the electron pair with it, so that the similarities are greater than the differences. Mechanisms that occur at a saturated carbon atom are considered first.<sup>1</sup> By far the most common are the S<sub>N</sub>1 and S<sub>N</sub>2 mechanisms.

### The S<sub>N</sub>2 Mechanism

The designation S<sub>N</sub>2 stands for *substitution nucleophilic bimolecular*. The IUPAC designation (p. 420) is A<sub>N</sub>D<sub>N</sub>. In this mechanism, there is *backside attack*:<sup>2</sup> the nucleophile approaches the substrate from a position 180° away from the leaving group. The reaction is a one-step process with no intermediate (see, however, pp. 428–431 and 440). The C–Y bond is formed as the C–X bond is broken to generate transition state **1**.



The energy necessary to break the C–X bond is supplied by simultaneous formation of the C–Y bond. The position of the atoms at the top of the curve of free energy of activation is represented as transition state **1**. Of course, the reaction does not stop here since this is the transition state. The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. When the transition state is reached, the central carbon atom has gone from its initial *sp*<sup>3</sup> hybridization to an *sp*<sup>2</sup> state with an approximately perpendicular *p* orbital. One lobe of this *p* orbital overlaps with the nucleophile and the other with the leaving group. This is why a frontside S<sub>N</sub>2 mechanism has never been observed. In a hypothetical frontside transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the *p* orbital. The backside mechanism involves the maximum amount of overlap throughout the course of the reaction. During the transition state the three nonreacting substituents and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and the leaving group are the same.

<sup>1</sup>For a monograph on this subject, see Hartshorn, S.R. *Aliphatic Nucleophilic Substitution*, Cambridge University Press, Cambridge, **1973**. For reviews, see Katritzky, A.R.; Brycki, B.E. *Chem. Soc. Rev.* **1990**, *19*, 83; Richard, J.P. *Adv. Carbocation Chem.* **1989**, *1*, 121; de la Mare, P.B.D.; Swedlund, B.E., in Patai, S. *The Chemistry of the Carbon–Halogen Bond*, pt. 1, Wiley, NY, **1973**, pp. 409–490. Streitwieser, A. *Solvolytic Displacement Reactions*, McGraw-Hill, NY, **1962**.

<sup>2</sup>See Sun, L.; Hase, W.L.; Song, K. *J. Am. Chem. Soc.* **2001**, *123*, 5753.