

Nucleophilicity and Basicity Factors in Organic Reactions

General Principles

Recall the definitions of electrophile and nucleophile:

Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.

Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Many functional groups have weakly electrophilic carbon atoms (colored red in the following examples). These include *alkyl halides* and *sulfonate esters* {**C**-X and **C**-OSO₂R}, as well as carbonyl compounds such as *aldehydes* and *ketones* {**C**=O}. These electrophilic functions may react with nucleophiles (bases) in two distinct ways:

- (i) Substitution or addition at carbon (this reflects nucleophilicity)
- (ii) β-Elimination or enolate anion formation (this reflects basicity)

Because these electrophilic reactants are weak, such reactions normally require strong nucleophiles or bases to proceed. However, if a preliminary ionization to a strongly electrophilic carbocation occurs: [C-X \longrightarrow C⁽⁺⁾ + X⁽⁻⁾]

or if the carbonyl group is converted to its more electrophilic conjugate acid: [C=O + A⁽⁺⁾ \longrightarrow ⁽⁺⁾C-O-A]

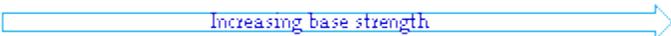
then reactions with much weaker nucleophiles or bases may take place.

Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it.

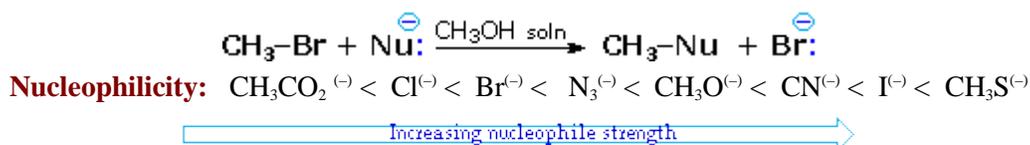
Basicity refers to the ability of a base to accept a **proton**. Basicity may be related to the pK_a of the corresponding conjugate acid, as shown below. The strongest bases have the weakest conjugate acids and *vice versa*. The range of basicities included in the following table is remarkable, covering over fifty powers of ten!

In an acid-base equilibrium the weakest acid and the weakest base will predominate (they will necessarily be on the same side of the equilibrium). Learning the pK_a values for common compounds provides a useful foundation on which to build an understanding of acid-base factors in reaction mechanisms.

Base	I ⁽⁻⁾	Cl ⁽⁻⁾	H ₂ O	CH ₃ CO ₂ ⁽⁻⁾	RS ⁽⁻⁾	CN ⁽⁻⁾	RO ⁽⁻⁾	NH ₂ ⁽⁻⁾	CH ₃ ⁽⁻⁾
Conj. Acid	HI	HCl	H ₃ O ⁽⁺⁾	CH ₃ CO ₂ H	RSH	HCN	ROH	NH ₃	CH ₄
pK_a	-9	-7	-1.7	4.8	8	9.1	16	33	48



Nucleophilicity is a more complex property. It commonly refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH₃-Br. Thus the nucleophilicity of the Nu:⁽⁻⁾ reactant in the following substitution reaction varies as shown in the chart below:



The reactivity range encompassed by these reagents is over 5,000 fold, thiolate being the most reactive. Clearly, there are significant differences between these nucleophilicities and the basicities discussed above.

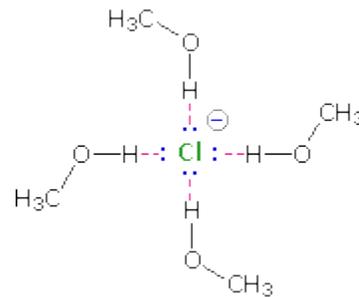
Some useful trends have been documented:

- (i) For a given element, negatively charged species are more nucleophilic (and basic) than are equivalent neutral species.
- (ii) For a given period of the periodic table, nucleophilicity (and basicity) decreases on moving from left to right.
- (iii) For a given group of the periodic table, nucleophilicity increases from top to bottom (*i.e.* with increasing size), although there is a solvent dependence due to hydrogen bonding. *Basicity varies in the opposite manner.*

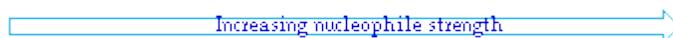
For two or more molecules incorporating nucleophilic atoms of the same kind and charge, the stronger base is usually the stronger nucleophile. Thus, 2,2,2-trifluoroethoxide (pK_a 12) is a weaker base and nucleophile than ethoxide (pK_a 16). A notable exception to this rule occurs when a vicinal (adjacent) atom carries a non-bonding electron pair. Two common examples of this exception, called **the alpha effect**, are hydroxide ion (pK_a 15.7) compared with hydroperoxide ion (pK_a 11.6), and ammonia (pK_a 9.3) compared with hydrazine (pK_a 8.0). In each of these pairs the weaker base is the stronger nucleophile.

Solvent Effects

Solvation of nucleophilic anions markedly influences their reactivity. The nucleophilicities cited above were obtained from reactions in methanol solution. Polar, protic solvents such as water and alcohols solvate anions by hydrogen bonding interactions, as shown in the diagram on the right. These solvated species are more stable and less reactive than the unsolvated "naked" anions. Polar, aprotic solvents such as DMSO (dimethyl sulfoxide), DMF (dimethylformamide) and acetonitrile do not solvate anions nearly as well as methanol, but provide good solvation of the accompanying cations. Consequently, most of the nucleophiles discussed here react more rapidly in solutions prepared from these solvents. These solvent effects are more pronounced for small basic anions than for large weakly basic anions. Thus, for reaction in DMSO solution we observe the following reactivity order:



Nucleophilicity: $I^{-} < Br^{-} < Cl^{-} \sim N_3^{-} < CH_3CO_2^{-} < CN^{-} \sim CH_3S^{-} < CH_3O^{-}$



Note that this order is roughly the order of increasing basicity (see above).

Source : <http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/react3.htm#rx10>